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(71) Applicant *(for all designated States except US)*: **KALYPSYS, INC.** [US/US]; 10420 Wateridge Circle, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SMITH, Nicholas, D.** [US/US]; 10420 Wateridge Circle, San Diego, CA 92121 (US). **BONNEFOUS, Celine** [FR/FR]; 10420 Wateridge Circle, San Diego, CA 92121 (US). **DURON, Sergio, G.** [US/US]; 10420 Wateridge Circle, San Diego, CA 92121 (US). **LINDSTROM, Andrew, K.** [US/US]; 10420 Wateridge Circle, San Diego, CA 92121 (US).

(74) Agents: **HATHAWAY, Cynthia** et al.; Global Patent Group, LLC, 10411 Clayton Road, Suite 304, St. Louis, MO 63131 (US).

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(54) Title: ISOQUINOLINES USEFUL AS INDUCIBLE NITRIC OXIDE SYNTHASE INHIBITORS

(57) Abstract: Disclosed herein are new isoquinoline compounds and compositions and their application as pharmaceuticals for the treatment of disease. Methods of inhibition of nitric oxide synthase activity in a human or animal subject are also provided for the treatment disease.

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ISOQUINOLINES USEFUL AS INDUCIBLE NITRIC OXIDE SYNTHASE INHIBITORS

[001] This application claims the benefit of priority of United States provisional application No. 60/891,034, filed February 21, 2007, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

[002] Disclosed herein are new isoquinoline compounds and compositions and their application as pharmaceuticals for the treatment of disease. Methods of inhibition of nitric oxide synthase activity in a human or animal subject are also provided for the treatment disease.

[003] Nitric oxide (NO) is involved in the regulation of many physiological processes as well as the pathophysiology of a number of diseases. It is synthesized enzymatically from L-arginine in numerous tissues and cell types by three distinct isoforms of the enzyme NO synthase (NOS). Two of these isoforms, endothelial NOS (eNOS) and neuronal NOS (nNOS) are expressed in a constitutive manner and are calcium/calmodulin dependent. Endothelial NOS is expressed by endothelium and other cell types and is involved in cardiovascular homeostasis. Neuronal NOS is constitutively present in both the central and peripheral nervous system where NO acts a neurotransmitter. Under normal physiological conditions, these constitutive forms of NOS generate low, transient levels of NO in response to increases in intracellular calcium concentrations. These low levels of NO act to regulate blood pressure, platelet adhesion, gastrointestinal motility, bronchomotor tone and neurotransmission.

[004] In contrast, the third isoform of NOS, inducible NOS (iNOS), a virtually calcium independent enzyme, is absent in resting cells, but is rapidly expressed in virtually all nucleated mammalian cells in response to stimuli such as endotoxins and/or cytokines. The inducible isoform is neither stimulated by calcium nor blocked by calmodulin antagonists. It contains several tightly bound co-factors, including FMN, FAD and tetrahydrobiopterin. The inducible isoform of nitric oxide synthase (NOS_2 or iNOS) is expressed in virtually all nucleated mammalian cells following exposure to inflammatory cytokines or lipopolysaccharide.

[005] The enzyme iNOS synthase is a homodimer composed of l30kDa subunits. Each subunit comprises an oxygenase domain and a reductase domain. Importantly, dimerization of the iNOS synthase is required for enzyme activity. If the dimerization mechanism is disrupted, the production of nitric oxide via inducible NOS enzyme is inhibited.

[006] The presence of iNOS in macrophages and lung epithelial cells is significant. Once present, iNOS synthesizes 100-1000 times more NO than the constitutive enzymes synthesize and does so for prolonged periods. This excessive production of NO and resulting NO-derived metabolites (*e.g.*, peroxynitrite) elicit cellular toxicity and tissue damage which contribute to the pathophysiology of a number of diseases, disorders and conditions.

[007] Nitric oxide generated by the inducible form of NOS has also been implicated in the pathogenesis of inflammatory diseases. In experimental animals, hypotension induced by lipopolysaccharide or tumor necrosis factor alpha can be reversed by NOS inhibitors. Conditions which lead to cytokine-induced hypotension include septic shock, hemodialysis and interleukin therapy in cancer patients. An iNOS inhibitor has been shown to be effective in treating cytokine-induced hypotension, inflammatory bowel disease, cerebral ischemia, osteoarthritis, asthma and neuropathies such as diabetic neuropathy and post-herpetic neuralgia.

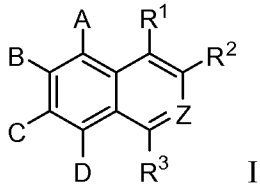
[008] In addition, nitric oxide localized in high amounts in inflamed tissues has been shown to induce pain locally and to enhance central as well as peripheral stimuli. Because nitric oxide produced by an inflammatory response is thought to be synthesized by iNOS, the inhibition of iNOS dimerization produces both prophylactic and remedial analgesia in patients.

[009] Hence, in situations where the overproduction of nitric oxide is deleterious, it would be advantageous to find a specific inhibitor of iNOS to reduce the production of NO. However, given the important physiological role played by the constitutive NOS isoform eNOS, which is expressed in endothelial tissues including vasculature, it is essential that the inhibition of iNOS has the least possible effect on the activity of eNOS, for example so as to avoid cardiovascular side effects. In contrast, nNOS crossover viewed to be much less a liability, and recent reports suggest that nNOS may

play an important role in the cetral nervous system component of pain perception (Boettger MK et al., Eur J Pain. 2007 Oct;11(7):810-8).

[010] Novel compounds and pharmaceutical compositions that inhibit NOS synthase, have been found together with methods of synthesizing and using the compounds including methods for the treatment of iNOS-mediated diseases in a patient by administering the compounds. In certain embodiments, the NOS inhibited is iNOS.

[011] Provided herein are compounds having structural Formula I:



I

or a salt, ester, or prodrug thereof, wherein:

Z is selected from the group consisting of N and N^+–O^-;

R^1 is selected from the group consisting of acyl, alkyl, alkylene, aminoalkyl, amidoalkyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkyl, arylalkoxy, arylamino, arylthio, carboxy, cycloalkyl, ester, ether, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylamino, heterocycloalkyl, heterocycloalkylalkyl, hydrazinyl, hydrogen, imino, thio, sulfonate, sulfonylamino and sulfonylaminoalkyl, any of which may be optionally substituted;

R^2 is selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkyl, alkylene, alkylamino, alkynyl, alkylimino, amido, amino, aryl, carboxy, cyano, cycloalkyl, ester, halo, haloalkyl, heteoaryl, heterocycloalkyl and hydrogen, any of which may be optionally substituted; or, alternatively, R^2 may combine with R^1 to form heterocycloalkyl, which may be optionally substituted;

R^3 is selected from the group consisting of acyl, alkoxy, alkyl, amino, halo, haloalkyl, cyano, and hydrogen, any of which may be optionally substituted; and

A, B, C and D are each independently selected from the group consisting of acyl, alkoxy, alkyl, alkylene, alkylamino, alkynyl, amido, amino, aminosulfonyl, aryl, arylalkoxy, arylamino, arylthio, carboxy, cycloalkyl, ester, ether, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylamino, heterocycloalkyl, hydrazinyl, hydrogen, imino,

thio, sulfonate and sulfonylamino, any of which may be optionally substituted; or, alternatively, any two or more A, B, C and D may combine to form aryl, cycloalkyl, heteroaryl or heterocycloalkyl, any of which may be optionally substituted.

[012] Certain compounds disclosed herein may possess useful NOS inhibiting activity, and may be used in the treatment or prophylaxis of a disease or condition in which NOS plays an active role. Thus, in broad aspect, certain embodiments also provide pharmaceutical compositions comprising one or more compounds disclosed herein together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. Certain embodiments provide methods for inhibiting NOS. Other embodiments provide methods for treating a NOS-mediated disorder in a patient in need of such treatment, comprising administering to said patient a therapeutically effective amount of a compound or composition as disclosed herein. Also provided is the use of certain compounds disclosed herein for use in the manufacture of a medicament for the treatment of a disease or condition ameliorated by the inhibition of NOS.

[013] In certain embodiments are provided compounds of either Formula I or Formula II, wherein:

R^1 is CH_2X^1;

X^1 is selected from the group consisting of CR^4R^5, $N(R^6)(R^7)$, $S(O)R^8$, $S(O)_2R^9$ or OR^{10};

R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are each independently selected from the group consisting of acyl, alkyl, alkylene, aminoalkyl, alkynyl, amido, amino, aryl, arylthio, carboxy, cycloalkyl, ester, ether, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylthio, heterocycloalkyl, heterocycloalkylthio, hydrogen, thio and sulfonyl, any of which may be optionally substituted; or, alternatively, R^6 and R^7 may combine to form heterocycloalkyl or heteroaryl, which may be optionally substituted;

A, B, C and D are each independently selected from the group consisting of acyl, alkoxy, alkyl, alkylene, alkylamino, alkynyl, amido, amino, aminosulfonyl,

carboxy, ester, ether, halo, haloalkoxy, haloalkyl, hydrogen, imino, thio, sulfonate and sulfonylamino, any of which may be optionally substituted.

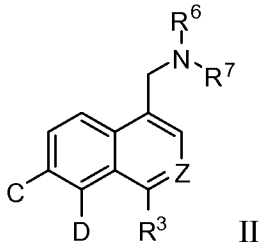
[014] In further embodiments are provided compounds of either Formula I or Formula II, wherein:

X^1 is $N(R^6)(R^7)$;

R^2 is hydrogen; and

A and B are both hydrogen.

[015] In certain embodiments, compounds have structural Formula II:



II

or a salt, ester, or prodrug thereof, wherein:

Z is selected from the group consisting of N and $N^+–O^-$;

R^3 is selected from the group consisting of lower alkoxy, lower alkyl, halo, lower haloalkyl, cyano, and hydrogen, any of which may be optionally substituted;

R^6 and R^7 are each independently selected from the group consisting of acyl, alkyl, alkylene, aminoalkyl, alkynyl, amido, amino, aryl, arylthio, carboxy, cycloalkyl, ester, ether, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylthio, heterocycloalkyl, heterocycloalkylthio, hydrogen, thio and sulfonyl, any of which may be optionally substituted; or, alternatively, R^6 and R^7 may combine to form heterocycloalkyl or heteroaryl, which may be optionally substituted; and

C and D are each independently selected from the group consisting of lower alkoxy, lower alkyl, halo, lower haloalkoxy, lower haloalkyl, and hydrogen, any of which may be optionally substituted.

[016] The compound as recited in Claim 4, or a salt, ester, or prodrug thereof, wherein:

R^6 is selected from the group consisting of acyl, alkyl, alkylene, aminoalkyl, alkynyl, amido, amino, aryl, arylthio, carboxy, cycloalkyl, ester, ether, halo,

haloalkoxy, haloalkyl, heteroaryl, heteroarylthio, heterocycloalkyl, heterocycloalkylthio, hydrogen, thio and sulfonyl, any of which may be optionally substituted; and

R^7 is selected from the group consisting of aryl and heteroaryl, either of which may be optionally substituted

[017] In further embodiments,

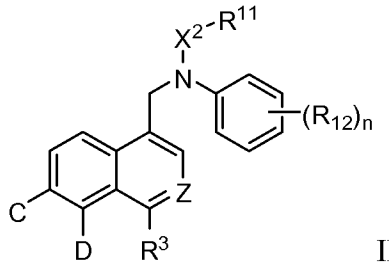
R^6 is X^2R^{11};

X^2 is selected from the group consisting of a bond, CH_2, C(O), and $S(O)_2$; and

R^{11} is selected from the group consisting of alkyl, amine, aryl, arylthio, cycloalkyl, haloalkyl, heteroaryl, heteroarylthio, heterocycloalkyl, and heterocycloalkylthio, any of which may be optionally substituted.

[018] In further embodiments, R^7 is phenyl.

[019] In certain embodiments, compounds have structural Formula III:



III

or a salt, ester, or prodrug thereof, wherein:

Z is selected from the group consisting of N and $N^+–O^-$;

R^3 is selected from the group consisting of acyl, alkoxy, alkyl, amino, halo, haloalkyl and hydrogen, any of which may be optionally substituted;

X^2 is selected from the group consisting of a bond, CH_2, C(O), and $S(O)_2$; and

R^{11} is selected from the group consisting of alkyl, amine, aryl, arylthio, cycloalkyl, haloalkyl, heteroaryl, heteroarylthio, heterocycloalkyl, and heterocycloalkylthio, any of which may be optionally substituted;

R^{12} is halogen;

n is 0, 1, or 2; and

C and D are each independently selected from the group consisting of lower alkoxy, lower alkyl, halo, lower haloalkoxy, lower haloalkyl, and hydrogen, any of which may be optionally substituted.

[020] In further embodiments, C and D are each independently selected from the group consisting of fluoro and hydrogen.

[021] In further embodiments, R^3 is selected from the group consisting of methyl, halo, cyano, and hydrogen, any of which may be optionally substituted.

[022] In further embodiments, R^3 is hydrogen.

[023] In further embodiments, R^{11} is selected from the group consisting of lower aryl and lower heteroaryl, either of which may be optionally substituted.

[024] In further embodiments, R^{11} is selected from the group consisting of pyridine, pyrimidine, pyrazine, pyridazine, and thiazole, any of which may be optionally substituted with one or more substituents selected from the group consisting of hydrogen, halogen, and methyl.

[025] In further embodiments, X^2 is selected from the group consisting of a bond and CH_2.

[026] In further embodiments, R^{12} is chloro and n is 1.

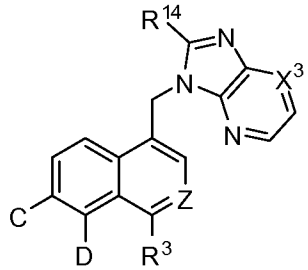
[027] In further embodiments, said chloro is attached in the meta-position.

[028] Also provided herein are compounds of either structural Formula III or structural Formula IV wherein:

R^6 and R^7 combine to form heteroaryl, which may be optionally substituted; and

C and D are each independently selected from the group consisting of lower alkoxy, lower alkyl, halo, lower haloalkoxy, lower haloalkyl, and hydrogen, any of which may be optionally substituted.

[029] In certain embodiments, compounds have structural Formula IV:



IV

or a salt, ester, or prodrug thereof, wherein:

Z is selected from the group consisting of N and $N^+–O^-$;

X^3 is selected from the group consisting of $C(R^{13})$ and N;

R^3 is selected from the group consisting of acyl, alkoxy, alkyl, amino, halo, haloalkyl and hydrogen, any of which may be optionally substituted;

R^{13} is selected from the group consisting of hydrogen, halogen, cyano, lower alkyl, lower alkoxy, lower amino, lower cycloalkyl, and lower heterocycloalkyl;

R^{14} is selected from the group consisting of alkyl, aryl, arylalkyl, amino, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of hydrogen, halogen, and methyl;

C and D are each independently selected from the group consisting of lower alkoxy, lower alkyl, halo, lower haloalkoxy, lower haloalkyl, and hydrogen, any of which may be optionally substituted.

[030] In further embodiments, C and D are each independently selected from the group consisting of fluoro and hydrogen.

[031] In further embodiments, R^3 is selected from the group consisting of methyl, halo, cyano, and hydrogen, any of which may be optionally substituted

[032] In further embodiments, R^3 is hydrogen.

[033] In further embodiments, R^{14} is selected from the group consisting of lower alkyl, lower aryl, lower arylalkyl, lower amino, lower cycloalkyl, lower cycloalkylalkyl, lower heteroaryl, lower heteroarylalkyl, lower heterocycloalkyl, and lower heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of hydrogen, halogen, and methyl;

[034] In further embodiments, R^{14} is selected from the group consisting of lower alkyl and lower cycloalkyl, either of which may be optionally substituted.

[035] In further embodiments, R^{13} is selected from the group consisting of hydrogen and methyl.

[036] Also provided herein are compounds selected from the group consisting of Examples 1 to 21.

[037] Also provided herein is a compound having either structural Formula I or structural Formula II for use as a medicament.

[038] Also provided herein is a compound having either structural Formula I or structural Formula II for use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the inhibition of iNOS.

[039] Also provided herein is a compound having either structural Formula I or structural Formula II together with a pharmaceutically acceptable carrier.

[040] Also provided herein is a method of inhibition of iNOS comprising contacting iNOS with a compound having either structural Formula I or structural Formula II.

[041] Also provided herein is a method of treatment of a iNOS-mediated disease comprising the administration of a therapeutically effective amount of a compound having either structural Formula I or structural Formula II to a patient in need thereof.

[042] In certain embodiments, said disease is selected from the group consisting of an inflammatory disease and a pain disorder.

[043] In further embodiments, said inflammatory disease is selected from the group consisting of psoriasis, inflammatory bowel disease, rheumatoid arthritis, atopic dermatitis, asthma, and chronic obstructive pulmonary disorder.

[044] In further embodiments, said pain is selected from the group consisting of neuropathic pain, migraine, and postsurgical pain.

[045] Also provided herein is a method of promoting wound healing in a patient in need thereof comprising the administration of a therapeutically effective amount of a compound having either structural Formula I or structural Formula II to said patient.

[046] Also provided herein is a method of treatment of a iNOS-mediated disease comprising the administration of:

a) a therapeutically effective amount of a compound having either structural Formula I or structural Formula II; and

b) another therapeutic agent.

[047] As used herein, the terms below have the meanings indicated.

[048] When ranges of values are disclosed, and the notation "from n_1 ... to n_2" is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range

may be integral or continuous between and including the end values. By way of example, the range "from 2 to 6 carbons" is intended to include two, three, four, five, and six carbons, since carbons come in integer units. Compare, by way of example, the range "from 1 to 3 μM (micromolar)," which is intended to include 1 μM, 3 μM, and everything in between to any number of significant figures (e.g., 1.255 μM, 2.1 μM, 2.9999 μM, etc.).

[049] The term "about," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[050] The term "acyl," as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety were the atom attached to the carbonyl is carbon. An "acetyl" group refers to a $-C(O)CH_3$ group. An "alkylcarbonyl" or "alkanoyl" group refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl. Examples of acyl groups include formyl, alkanoyl and aroyl.

[051] The term "alkenyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkenyl will comprise from 2 to 6 carbon atoms. The term "alkenylene" refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [(–CH=CH–),(–C::C–)]. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like. Unless otherwise specified, the term "alkenyl" may include "alkenylene" groups.

[052] The term "alkoxy," as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable

alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

[053] The term "alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to 20 carbon atoms. In certain embodiments, said alkyl will comprise from 1 to 10 carbon atoms. In further embodiments, said alkyl will comprise from 1 to 6 carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term "alkylene," as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene (–CH_2–). Unless otherwise specified, the term "alkyl" may include "alkylene" groups.

[054] The term "alkylamino," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino and the like.

[055] The term "alkylidene," as used herein, alone or in combination, refers to an alkenyl group in which one carbon atom of the carbon-carbon double bond belongs to the moiety to which the alkenyl group is attached.

[056] The term "alkylthio," as used herein, alone or in combination, refers to an alkyl thioether (R–S–) radical wherein the term alkyl is as defined above and wherein the sulfur may be singly or doubly oxidized. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, methanesulfonyl, ethanesulfinyl, and the like.

[057] The term "alkynyl," as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkynyl comprises from 2 to 6 carbon atoms. In further embodiments, said alkynyl comprises from 2 to 4 carbon atoms. The term "alkynylene" refers to a carbon-carbon triple bond attached at two positions such as ethynylene (–C:::C–, –C≡C–). Examples of alkynyl

radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, 3-methylbutyn-1-yl, hexyn-2-yl, and the like. Unless otherwise specified, the term "alkynyl" may include "alkynylene" groups.

[058] The terms "amido" and "carbamoyl,"as used herein, alone or in combination, refer to an amino group as described below attached to the parent molecular moiety through a carbonyl group, or vice versa. The term "C-amido" as used herein, alone or in combination, refers to a -C(=O)-NR_2 group with R as defined herein. The term "N-amido" as used herein, alone or in combination, refers to a RC(=O)NH- group, with R as defined herein. The term "acylamino" as used herein, alone or in combination, embraces an acyl group attached to the parent moiety through an amino group. An example of an "acylamino" group is acetylamino ($CH_3C(O)NH$–).

[059] The term "amino," as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently selected from the group consisting of hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted. Additionally, R and R' may combine to form an N-containing heterocycloalkyl, either of which may be optionally substituted.

[060] The term "aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such polycyclic ring systems are fused together. The term "aryl" embraces aromatic groups such as phenyl, naphthyl, anthracenyl, and phenanthryl.

[061] The term "arylalkenyl" or "aralkenyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

[062] The term "arylalkoxy" or "aralkoxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[063] The term "arylalkyl" or "aralkyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

[064] The term "arylalkynyl" or "aralkynyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

[065] The term "arylalkanoyl" or "aralkanoyl" or "aroyl,"as used herein, alone or in combination, refers to an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, napthoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, and the like.

[066] The term aryloxy as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxy.

[067] The terms "benzo" and "benz," as used herein, alone or in combination, refer to the divalent radical C_6H_4= derived from benzene. Examples include benzothiophene and benzimidazole.

[068] The term "carbamate," as used herein, alone or in combination, refers to an ester of carbamic acid (–NHCOO–) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which may be optionally substituted as defined herein.

[069] The term "O-carbamyl" as used herein, alone or in combination, refers to a -OC(O)NRR', group-with R and R' as defined herein.

[070] The term "N-carbamyl" as used herein, alone or in combination, refers to a ROC(O)NR'- group, with R and R' as defined herein.

[071] The term "carbonyl," as used herein, when alone includes formyl [–C(O)H] and in combination is a –C(O)– group.

[072] The term "carboxyl" or "carboxy," as used herein, refers to –C(O)OH or the corresponding "carboxylate" anion, such as is in a carboxylic acid salt. An "O-carboxy" group refers to a RC(O)O– group, where R is as defined herein. A "C-carboxy" group refers to a –C(O)OR groups where R is as defined herein.

[073] The term "cyano," as used herein, alone or in combination, refers to –CN.

[074] The term "cycloalkyl," or, alternatively, "carbocycle," as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl group wherein each cyclic moiety contains from 3 to 12 carbon atom

ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. In certain embodiments, said cycloalkyl will comprise from 5 to 7 carbon atoms. Examples of such cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronapthyl, indanyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. "Bicyclic" and "tricyclic" as used herein are intended to include both fused ring systems, such as decahydronaphthalene, octahydronaphthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by, bicyclo[1,1,1]pentane, camphor, adamantane, and bicyclo[3,2,1]octane.

[075] The term "ester," as used herein, alone or in combination, refers to a carboxy group bridging two moieties linked at carbon atoms.

[076] The term "ether," as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

[077] The term "halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

[078] The term "haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[079] The term "haloalkyl," as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene (–CFH–), difluoromethylene ($–CF_2–$), chloromethylene (–CHCl–) and the like.

[080] The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$.

[081] The term "heteroaryl," as used herein, alone or in combination, refers to a 3 to 7 membered unsaturated heteromonocyclic ring, or a fused monocyclic, bicyclic, or tricyclic ring system in which at least one of the fused rings is aromatic, which contains at least one atom selected from the group consisting of O, S, and N. In certain embodiments, said heteroaryl will comprise from 5 to 7 carbon atoms. The term also embraces fused polycyclic groups wherein heterocyclic rings are fused with aryl rings, wherein heteroaryl rings are fused with other heteroaryl rings, wherein heteroaryl rings are fused with heterocycloalkyl rings, or wherein heteroaryl rings are fused with cycloalkyl rings. Examples of heteroaryl groups include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, pyranyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, benzothienyl, chromonyl, coumarinyl, benzopyranyl, tetrahydroquinolinyl, tetrazolopyridazinyl, tetrahydroisoquinolinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[082] The terms “heterocycloalkyl” and, interchangeably, “heterocycle,” as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated monocyclic, bicyclic, or tricyclic heterocyclic group containing at least one heteroatom as a ring member, wherein each said heteroatom may be independently

selected from the group consisting of nitrogen, oxygen, and sulfur In certain embodiments, said hetercycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said hetercycloalkyl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said hetercycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, said hetercycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, said hetercycloalkyl will comprise from 5 to 6 ring members in each ring. "Heterocycloalkyl" and "heterocycle" are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Examples of heterocycle groups include aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihy-dropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups may be optionally substituted unless specifically prohibited.

[083] The term "hydrazinyl" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., –N–N–.

[084] The term "hydroxy," as used herein, alone or in combination, refers to –OH.

[085] The term "hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

[086] The term "imino," as used herein, alone or in combination, refers to =N–.

[087] The term "iminohydroxy," as used herein, alone or in combination, refers to =N(OH) and =N–O–.

[088] The phrase "in the main chain" refers to the longest contiguous or adjacent chain of carbon atoms starting at the point of attachment of a group to the compounds of any one of the formulas disclosed herein.

[089] The term "isocyanato" refers to a –NCO group.

[090] The term "isothiocyanato" refers to a –NCS group.

[091] The phrase "linear chain of atoms" refers to the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

[092] The term "lower," as used herein, alone or in a combination, where not otherwise specifically defined, means containing from 1 to and including 6 carbon atoms.

[093] The term "lower aryl," as used herein, alone or in combination, means phenyl or naphthyl, which may be optionally substituted as provided.

[094] The term "lower heteroaryl," as used herein, alone or in combination, means either 1) monocyclic heteroaryl comprising five or six ring members, of which between one and four said members may be heteroatoms selected from the group consisting of O, S, and N, or 2) bicyclic heteroaryl, wherein each of the fused rings comprises five or six ring members, comprising between them one to four heteroatoms selected from the group consisting of O, S, and N.

[095] The term "lower cycloalkyl," as used herein, alone or in combination, means a monocyclic cycloalkyl having between three and six ring members. Lower cycloalkyls may be unsaturated. Examples of lower cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[096] The term "lower heterocycloalkyl," as used herein, alone or in combination, means a monocyclic heterocycloalkyl having between three and six ring members, of which between one and four may be heteroatoms selected from the group consisting of O, S, and N. Examples of lower heterocycloalkyls include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, and morpholinyl. Lower heterocycloalkyls may be unsaturated.

[097] The term "lower amino," as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently selected from the group consisting of hydrogen, lower alkyl, and lower heteroalkyl, any of which may be optionally substituted. Additionally, the R and R' of a lower amino group may combine to form a five- or six-membered heterocycloalkyl, either of which may be optionally substituted.

[098] The term "mercaptyl" as used herein, alone or in combination, refers to an RS– group, where R is as defined herein.

[099] The term "nitro," as used herein, alone or in combination, refers to $-NO_2$.

[0100] The terms "oxy" or "oxa," as used herein, alone or in combination, refer to –O–.

[0101] The term "oxo," as used herein, alone or in combination, refers to =O.

[0102] The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

[0103] The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

[0104] The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer the $–SO_3H$ group and its anion as the sulfonic acid is used in salt formation.

[0105] The term "sulfanyl," as used herein, alone or in combination, refers to –S–.

[0106] The term "sulfinyl," as used herein, alone or in combination, refers to –S(O)–.

[0107] The term "sulfonyl," as used herein, alone or in combination, refers to $–S(O)_2–$.

[0108] The term "N-sulfonamido" refers to a $RS(=O)_2NR'$- group with R and R' as defined herein.

[0109] The term "S-sulfonamido" refers to a $-S(=O)_2NRR'$, group, with R and R' as defined herein.

[0110] The terms "thia" and "thio," as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

[0111] The term "thiol," as used herein, alone or in combination, refers to an –SH group.

[0112] The term "thiocarbonyl," as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.

[0113] The term "N-thiocarbamyl" refers to an ROC(S)NR'– group, with R and R'as defined herein.

[0114] The term "O-thiocarbamyl" refers to a –OC(S)NRR', group with R and R'as defined herein.

[0115] The term "thiocyanato" refers to a –CNS group.

[0116] The term "trisubstituted silyl," as used herein, alone or in combination, refers to a silicone group substituted at its three free valences with groups as listed herein under the definition of substituted amino. Examples include trimethysilyl, tert-butyldimethylsilyl, triphenylsilyl and the like.

[0117] Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

[0118] When a group is defined to be "null," what is meant is that said group is absent.

[0119] The term "optionally substituted" means the anteceding group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, lower haloalkylthio, lower perhaloalkylthio, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3, SH, SCH_3, $C(O)CH_3$, CO_2CH_3, CO_2H, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., $-CH_2CF_3$).

Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with."

[0120] The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety selected from the group consisting of hydrogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R^n where n=(1, 2, 3, ...n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. Thus, by way of example only, an unsymmetrical group such as –C(O)N(R)– may be attached to the parent moiety at either the carbon or the nitrogen.

[0121] Asymmetric centers exist in the compounds disclosed herein. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms,as well as d-isomers and 1-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral

chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds disclosed herein may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Additionally, the compounds disclosed herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms.

[0122] The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

[0123] The term "disease" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder" and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

[0124] The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0125] The term “inducible nitric oxide synthase inhibitor" or “iNOS inhibitor” is used herein to refer to a compound that exhibits an IC_{50} with respect to iNOS of no more than about 100 μM and more typically not more than about 50 μM, as measured in the iNOS DAN assay described generally hereinbelow. "IC_{50}" is that concentration of inhibitor which reduces the activity of an enzyme (e.g., iNOS) to half-maximal level. Certain compounds disclosed herein have been discovered to exhibit inhibition against iNOS. In certain embodiments, compounds will exhibit an EC_{50} with respect to iNOS of no more than about 10 μM; in further embodiments, compounds will exhibit an EC_{50} with respect to iNOS of no more than about 5 μM; in yet further embodiments, compounds will exhibit an EC_{50} with respect to iNOS of not more than about 1 μM; in yet further embodiments, compounds will exhibit an EC_{50} with respect to iNOS of not more than about 200 nM, as measured in the iNOS assay described herein.

[0126] The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder. This amount will achieve the goal of reducing or eliminating the said disease or disorder.

[0127] The term “therapeutically acceptable” refers to those compounds (or salts, prodrugs, tautomers, zwitterionic forms, etc.) which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0128] As used herein, reference to "treatment" of a patient is intended to include prophylaxis. The term “patient” means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits. Preferably, the patient is a human.

[0129] The term "prodrug" refers to a compound that is made more active in vivo. Certain compounds disclosed herein may also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism : Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be

converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

[0130] The compounds disclosed herein can exist as therapeutically acceptable salts. The present invention includes compounds listed above in the form of salts, including acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Basic addition salts may also be formed and be pharmaceutically acceptable. For a more complete discussion of the preparation and selection of salts, refer to *Pharmaceutical Salts: Properties, Selection, and Use* (Stahl, P. Heinrich. Wiley-VCHA, Zurich, Switzerland, 2002).

[0131] The term “therapeutically acceptable salt,” as used herein, represents salts or zwitterionic forms of the compounds disclosed herein which are water or oil-soluble or dispersible and therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate),

lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds disclosed herein can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds disclosed herein, and the like.

[0132] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0133] While it may be possible for a compound disclosed herein to be administered as the raw chemical, it is also possible to present it as a pharmaceutical formulation. Accordingly, provided herein are pharmaceutical formulations which comprise one or more of certain compounds disclosed herein, or one or more

pharmaceutically acceptable salts, esters, prodrugs, amides, or solvates thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences. The pharmaceutical compositions disclosed herein may be manufactured in any manner known in the art, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0134] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Typically, these methods include the step of bringing into association a compound or a pharmaceutically acceptable salt, ester, amide, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0135] Formulations of the compounds disclosed herein suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0136] Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0137] The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free

water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0138] Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0139] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0140] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

[0141] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

[0142] Certain compounds disclosed herein may be administered topically, that is by non-systemic administration. This includes the application of a compound disclosed herein externally to the epidermis or the buccal cavity and the instillation of such a

compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

[0143] Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient for topical administration may comprise, for example, from 0.001% to 10% w/w (by weight) of the formulation. In certain embodiments, the active ingredient may comprise as much as 10% w/w. In other embodiments, it may comprise less than 5% w/w. In certain embodiments, the active ingredient may comprise from 2% w/w to 5% w/w. In other embodiments, it may comprise from 0.1% to 1% w/w of the formulation.

[0144] Gels for topical or transdermal administration may comprise, generally, a mixture of volatile solvents, nonvolatile solvents, and water. In certain embodiments, the volatile solvent component of the buffered solvent system may include lower (C1-C6) alkyl alcohols, lower alkyl glycols and lower glycol polymers. In further embodiments, the volatile solvent is ethanol. The volatile solvent component is thought to act as a penetration enhancer, while also producing a cooling effect on the skin as it evaporates. The nonvolatile solvent portion of the buffered solvent system is selected from lower alkylene glycols and lower glycol polymers. In certain embodiments, propylene glycol is used. The nonvolatile solvent slows the evaporation of the volatile solvent and reduces the vapor pressure of the buffered solvent system. The amount of this nonvolatile solvent component, as with the volatile solvent, is determined by the pharmaceutical compound or drug being used. When too little of the nonvolatile solvent is in the system, the pharmaceutical compound may crystallize due to evaporation of volatile solvent, while an excess may result in a lack of bioavailability due to poor release of drug from solvent mixture. The buffer component of the buffered solvent system may be selected from any buffer commonly used in the art; in certain embodiments, water is used. A common ratio of ingredients is about 20% of the nonvolatile solvent, about 40% of the volatile solvent, and about 40% water. There are several optional ingredients which can be added to the topical

composition. These include, but are not limited to, chelators and gelling agents. Appropriate gelling agents can include, but are not limited to, semisynthetic cellulose derivatives (such as hydroxypropylmethylcellulose) and synthetic polymers, and cosmetic agents.

[0145] Lotions include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

[0146] Creams, ointments or pastes are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

[0147] Drops may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and, in certain embodiments, including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the

drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

[0148] Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

[0149] For administration by inhalation, compounds may be conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[0150] Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof, of the active ingredient.

[0151] It should be understood that in addition to the ingredients particularly mentioned above, the formulations described above may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0152] Compounds may be administered orally or via injection at a dose of from 0.1 to 500 mg/kg per day. The dose range for adult humans is generally from 5 mg to 2 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of one or more compounds which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

[0153] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

[0154] The compounds can be administered in various modes, *e.g.* orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity.

[0155] In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[0156] Specific, non-limiting examples of possible combination therapies include use of the compounds disclosed herein with: a) corticosteroids including betamethasone dipropionate (augmented and nonaugemnted), betamethasone valerate, clobetasol propionate, diflorasone diacetate, halobetasol propionate, amcinonide, dexosimethasone, fluocinolone acetononide, fluocinonide, halocinonide, clocortalone pivalate, dexosimetasone, and flurandrenalide; b) non-steroidal anti-inflammatory drugs including diclofenac, ketoprofen, and piroxicam; c) muscle relaxants and combinations thereof with other agents, including cyclobenzaprine, baclofen, cyclobenzaprine/lidocaine, baclofen/cyclobenzaprine, and cyclobenzaprine/lidocaine/ketoprofen; d) anaesthetics and combinations thereof with other agents, including lidocaine, lidocaine/deoxy-D-glucose (an antiviral), prilocaine, and EMLA Cream [Eutectic Mixture of Local Anesthetics (lidocaine 2.5% and prilocaine 2.5%; an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather then as crystals)]; e) expectorants and combinations thereof with other agents, including guaifenesin and guaifenesin/ketoprofen/cyclobenzaprine; f) antidepressants including tricyclic antidepressants (*e.g.*, amitryptiline, doxepin, desipramine, imipramine, amoxapine, clomipramine, nortriptyline, and protriptyline), selective serotonin/norepinephrine reuptake inhibitors including (*e.g*, duloxetine and mirtazepine), and selective norepinephrine reuptake inhibitors (*e.g.*, nisoxetine, maprotiline, and reboxetine), selective serotonin reuptake inhibitors (*e.g.*, fluoxetine and fluvoxamine); g) anticonvulsants and combinations thereof, including gabapentin, carbamazepine, felbamate, lamotrigine, topiramate, tiagabine, oxcarbazepine, carbamezipine, zonisamide, mexiletine, gabapentin/clonidine, gabapentin/carbamazepine, and carbamazepine/cyclobenzaprine; h) antihypertensives including clonidine; i) opioids including loperamide, tramadol, morphine, fentanyl, oxycodone, levorphanol, and butorphanol; j) topical counter-irritants including menthol, oil of wintergreen, camphor, eucalyptus oil and turpentine oil; k) topical cannabinoids including selective and non-selective CB1/CB2 ligands; and other agents, such as capsaicin.

[0157] In any case, the multiple therapeutic agents (at least one of which is a compound disclosed herein) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

[0158] Thus, in another aspect, the provided herein are methods for treating iNOS-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound as disclosed herein effective to reduce or prevent said disorder in the subject in combination with at least one additional agent for the treatment of said disorder that is known in the art. In a related aspect, provided herein are therapeutic compositions comprising at least one compound as disclosed herein in combination with one or more additional agents for the treatment of iNOS-mediated disorders.

[0159] Compounds disclosed herein are useful in treating nitric oxide synthase-mediated disease, disorders and conditions, and are particularly suitable as inhibitors of nitric oxide synthase. The compounds are useful to treat patients with neuropathy or inflammatory pain such as reflex sympathetic dystrophy/causalgia (nerve injury), peripheral neuropathy (including diabetic neuropathy), intractable cancer pain, complex regional pain syndrome, and entrapment neuropathy (carpel tunnel syndrome) (DeAlba J et al., *Pain*. 2006 Jan;120(1-2):170-81; Levy D et al., *Neurosci Lett*. 1999 Feb 5;260(3):207-9). The compounds are also useful in the treatment of pain associated with acute herpes zoster (shingles), postherpetic neuralgia (PHN), and associated pain syndromes such as ocular pain. The compounds are further useful as analgesics in the treatment of pain such as surgical analgesia, or as an antipyretic for the treatment of fever. Pain indications include, but are not limited to, post-surgical pain for various surgical procedures including post-cardiac surgery, dental pain/dental extraction, pain resulting from cancer, muscular pain, mastalgia, pain resulting from dermal injuries, lower back pain, headaches of various etiologies including migraine headaches (Ramadan NM, Buchanan TM: *Pharmacol Ther*. 2006 Oct;112(1):199-212),

and the like. The compounds are also useful for the treatment of pain-related disorders such as tactile allodynia and hyperalgesia (LaBuda, CJ et al., *Eur J Pain*. 2006 Aug;10(6):505-12). The pain may be somatogenic (either nociceptive or neuropathic), acute and/or chronic. The nitric oxide inhibitors disclosed herein are also useful in conditions where NSAIDs, morphine or fentanyl opiates and/or other opioid analgesics would traditionally be administered.

[0160] Furthermore, the compounds disclosed herein can be used in the treatment or prevention of opiate tolerance in patients needing protracted opiate analgesics, and benzodiazepine tolerance in patients taking benzodiazepines, and other addictive behavior, for example, nicotine addiction, alcoholism, and eating disorders. Moreover, the compounds and methods disclosed herein are useful in the treatment or prevention of drug withdrawal symptoms, for example treatment or prevention of symptoms of withdrawal from opiate (Herman BH et al., *Neuropsychopharmacology*. 1995 Dec;13(4):269-93), alcohol (Adams ML, Cicero TJ: *Alcohol*. 1998 Aug;16(2):153-8), or tobacco (Vleeming W et al., *Nicotine Tob Res*. 2002 Aug;4(3):341-8)addiction.

[0161] In addition, the compounds disclosed herein can be used to treat insulin resistance and other metabolic disorders such as atherosclerosis that are typically associated with an exaggerated inflammatory signaling.

[0162] Further, the compounds disclosed herein can be used to treat respiratory diseases, including therapeutic methods of use in medicine for preventing and treating a respiratory disease or condition including: asthmatic conditions including allergen-induced asthma, exercise-induced asthma, pollution-induced asthma, cold-induced asthma, and viral-induced-asthma; chronic obstructive pulmonary diseases including chronic bronchitis with normal airflow, chronic bronchitis with airway obstruction (chronic obstructive bronchitis), emphysema, asthmatic bronchitis, and bullous disease; and other pulmonary diseases involving inflammation including bronchioectasis cystic fibrosis, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome, pneumonia, aspiration or inhalation injury, fat embolism in the lung, acidosis inflammation of the lung, acute pulmonary edema, acute mountain sickness, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism,

heparin-protamine reactions, sepsis, status asthamticus and hypoxia (Barnes PJ et al., *Immunol Today*. 1995 Mar;16(3):128-30).

[0163] Other disorders or conditions which can be advantageously treated by the compounds disclosed herein include inflammation (Nussler AK, Billiar TR: *J Leukoc Biol.* 1993 Aug;54(2):171-8) and related diseases, including autoimmune diseases (Kolb H, Kolh-Bachofen B: *Immunol Today*. 1992 May;13(5):157-60). The compounds are useful as anti-inflammatory agents with the additional benefit of having significantly less harmful side effects. The compounds are useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, and pyogenic arthritis. The compounds are also useful in treating osteoporosis and other related bone disorders. These compounds can also be used to treat gastrointestinal conditions such as reflux esophagitis, diarrhea, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. The compounds may also be used in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. In addition, compounds disclosed herein are also useful in organ transplant patients either alone or in combination with conventional immunomodulators. Yet further, the compounds disclosed hereinare useful in the treatment of pruritis and vitaligo.

[0164] The compounds disclosed herein are also useful in treating tissue damage in such diseases as vascular diseases, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephritis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, periodontis, hypersensitivity, swelling occurring after injury, ischemias including myocardial ischemia, cardiovascular ischemia, and ischemia secondary to cardiac arrest, and the like (Abramson SB et al., *Best Pract Res Clin Rheumatol.* 2001 Dec;15(5):831-45).

[0165] The compounds disclosed herein are also useful for the treatment of certain diseases and disorders of the nervous system. Central nervous system disorders in

which nitric oxide inhibition is useful include cortical dementias including Alzheimer's disease, central nervous system damage resulting from stroke, ischemias including cerebral ischemia (both focal ischemia, thrombotic stroke and global ischemia (for example, secondary to cardiac arrest), and trauma (Samdani AF et al., *Stroke*. 1997 Jun;28(6):1283-8). Neurodegenerative disorders in which nitric oxide inhibition is useful include nerve degeneration or nerve necrosis in disorders such as hypoxia, hypoglycemia, epilepsy, and in cases of central nervous system (CNS) trauma (such as spinal cord and head injury), hyperbaric oxygen convulsions and toxicity, dementia e.g. pre-senile dementia, and AIDS-related dementia, cachexia, Sydenham's chorea, Huntington's disease, Parkinson's Disease, amyotrophic lateral sclerosis (ALS), Korsakoffs disease, imbecility relating to a cerebral vessel disorder, sleeping disorders, schizophrenia, depression, depression or other symptoms associated with Premenstrual Syndrome (PMS), and anxiety.

[0166] Furthermore, the compounds disclosed herein are also useful in inhibiting NO production from L-arginine including systemic hypotension associated with septic and/or toxic hemorrhagic shock induced by a wide variety of agents (Vallance P. et al., *New Horiz.* 1993 Feb;1(1):77-86); therapy with cytokines such as TNF, IL-1 and IL-2; and as an adjuvant to short term immunosuppression in transplant therapy. These compounds can also be used to treat allergic rhinitis, respiratory distress syndrome, endotoxic shock syndrome, and atherosclerosis.

[0167] Still other disorders or conditions advantageously treated by the compounds disclosed herein include the prevention or treatment of hypreproliferative diseases, especially cancers. Hematological and non-hematological malignancies which may be treated or prevented include but are not limited to multiple myeloma, acute and chronic leukemias including Acute Lymphocytic Leukemia (ALL), Chronic Lymphocytic Leukemia (CLL), and Chronic Myelogenous Leukemia(CLL), lymphomas, including Hodgkin's lymphoma and non-Hodgkin's lymphoma (low, intermediate, and high grade), as well as solid tumors and malignancies of the brain, head and neck, breast, lung, reproductive tract, upper digestive tract, pancreas, liver, renal, bladder, prostate and colorectal. The present compounds and methods can also be used to treat the fibrosis, such as that which occurs with radiation therapy. The present compounds and

methods can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, the present compounds and methods can be used to prevent polyps from forming in patients at risk of FAP.

[0168] The compounds disclosed herein can be used in the treatment of ophthalmic diseases, such as glaucoma, retinal ganglion degeneration, ocular ischemia, retinitis, retinopathies, uveitis, ocular photophobia, and of inflammation and pain associated with acute injury to the eye tissue. Specifically, the compounds can be used to treat glaucomatous retinopathy and/or diabetic retinopathy. The compounds can also be used to treat post-operative inflammation or pain as from ophthalmic surgery such as cataract surgery and refractive surgery.

[0169] Moreover, compounds disclosed herein may be used in the treatment of menstrual cramps, dysmenorrhea, premature labor, tendonitis, bursitis, skin-related conditions such as psoriasis, eczema, burns, sunburn, dermatitis, pancreatitis, hepatitis, and the like. Other conditions in which the compounds provide an advantage in inhibiting nitric oxide inhibition include diabetes (type I or type II), congestive heart failure, myocarditis, atherosclerosis, and aortic aneurysm.

[0170] The present compounds may also be used in co-therapies, partially or completely, in place of other conventional anti-inflammatory therapies, such as together with steroids, NSAIDs, COX-2 selective inhibitors, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors. The compounds disclosed herein may also be used to prevent tissue damage when therapeutically combined with antibacterial or antiviral agents.

[0171] Besides being useful for human treatment, certain compounds and formulations disclosed herein may also be useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

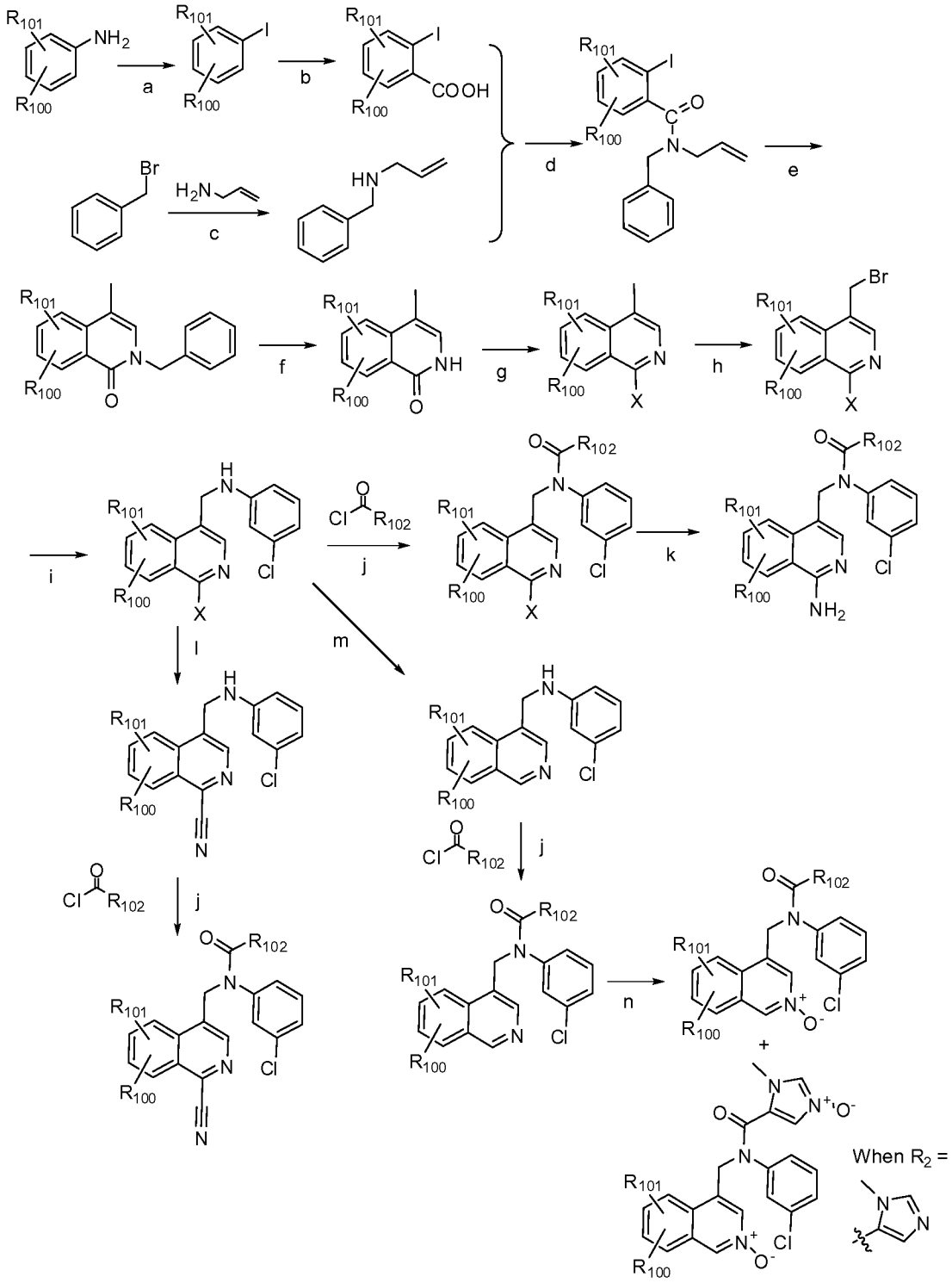
[0172] All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein in their entireties. Where any inconsistencies arise, material literally disclosed herein controls.

Attorney Docket No. K0034-401-PC

General Synthetic Methods for Preparing Compounds

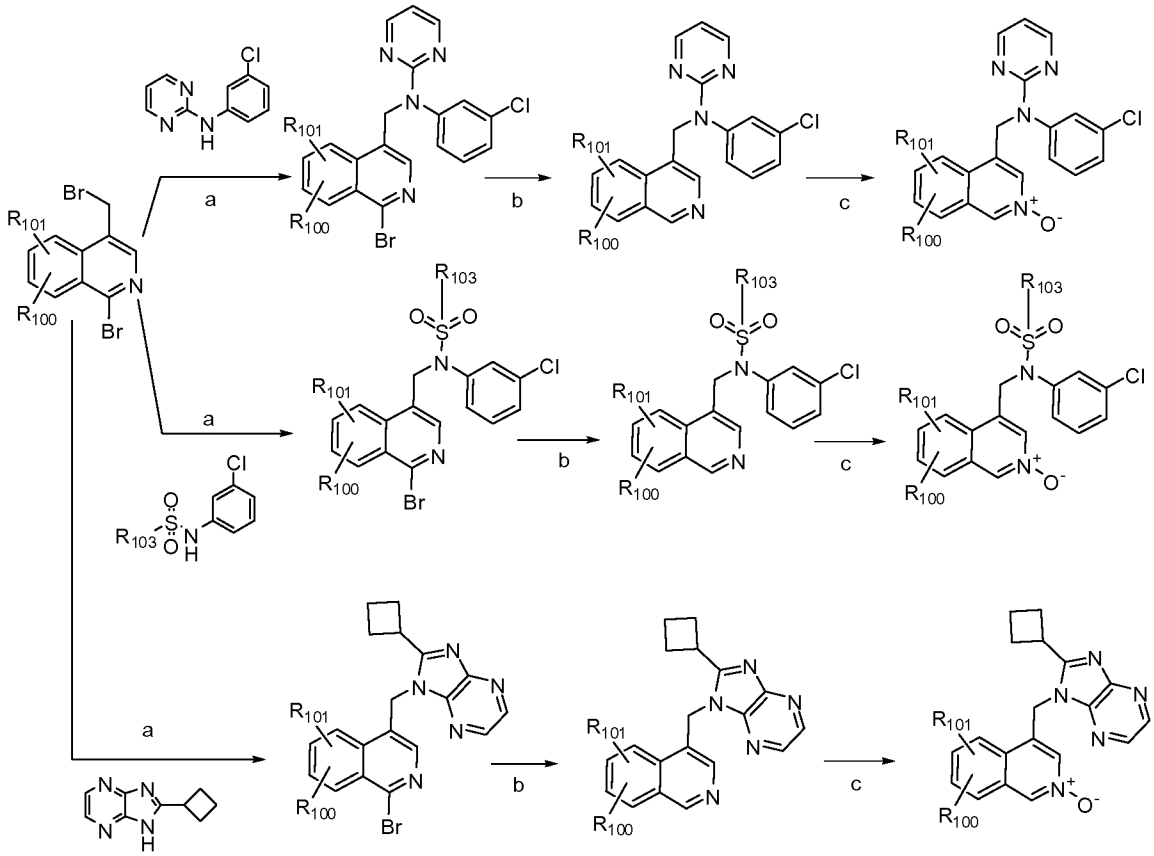
[0173] The following schemes can be used to practice the present invention.

[0174] **Scheme 1**



[0175] Reagents: (a) $NaNO_2$, H_2SO_4, KI, water, 0°C, 2 h. (b) (i) *n*-BuLi, diisopropylamine, ether, -70°C 1 h. (ii) CO_2, -50°C, 1 h. (c) prop-2-en-1-amine, RT, 18 h. (d) (i) $SOCl_2$, 80°C, 1.5 h. (ii) triethylamine, THF, 5°C to RT, 2 h. (e) dicyclohexylamine, triphenylphosphine, $Pd(OAc)_2$, DMA, 100°C, 18 h. (f) H_2SO_4, 150°C, 2.5 h. (g) POX_3, PX_3, 120°C, 4 h. (h) 1-bromopyrrolidine-2,5-dione, 2,2-Azobis(isobutyronitrile), CCl_4, 80°C, 2 h. (i) base, DMF, 40°C, 2 h. (j) $R_{102}COCl$, DMF, 0°C, 1 h. (k) $NH_3.H_2O$, CHO-NH_2, EtOH, 100°C, 1 h. (l) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 80°C, 2 h. (m) Pd/C, H_2, MeOH, 4 h, RT. (n) *m*-CPBA, DCM, RT, 1 h.

[0176] **Scheme 2**

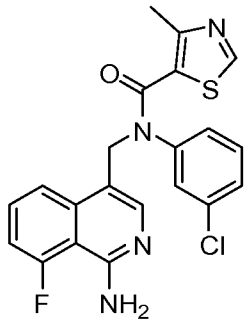


[0177] Reagents: (a) Base, DMF, RT°C, 1 to 18 h. (b) Pd/C, H_2, MeOH, 8 h, RT. (c) *m*-CPBA, DCM, RT, 1 h.

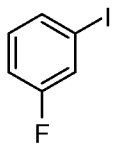
[0178] The invention is further illustrated by the following examples.

EXAMPLE 1

N-((1-Amino-8-fluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)-4-methylthiazole-5-carboxamide



Step 1: **1-Fluoro-3-iodobenzene**



$NaNO_2$ (6.4 g, 92.75 mmol) in water (20 mL) was added to a solution of 3-fluoroaniline (10 g, 90.09 mmol) in 32% H_2SO_4 (179 g) at 0°C. The resulting mixture was stirred at 0°C for 1 h. This was followed by the addition of a solution of KI (22.4 g, 134.94 mmol) in water (30 mL) while cooling to 0°C and the resulting reaction mixture was stirred at 0°C for 1 h. The aqueous solution was extracted with EtOAc (2x250 mL). The organics were combined, washed with water (5x200 mL) and 10% $NaHSO_3$ (3x 200 mL), dried over Na_2SO_4, and evaporated to dryness to afford 17.7 g (82%) of 1-fluoro-3-iodobenzene as a yellow solid.

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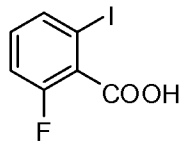
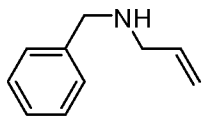
Step 2: **2-Fluoro-6-iodobenzoic acid (Intermediate A)**



n-BuLi (120 mL) was added dropwise to a solution of diisopropylamine (33.33 g, 330.00 mmol) in ether (300 mL) at -70°C. The resulting solution was stirred at -70°C for 1 h followed by addition of a solution of 1-fluoro-3-iodobenzene (22.2 g, 100.00 mmol) in ether (100 mL). After stirring for 1 h (at -70°C), CO_2 (gas) was bubbled in the reaction mixture. The resulting solution was stirred at -50°C for 1 h. The resulting solution was extracted with water (1x300 mL). Adjustment of the pH to 1 was accomplished by the addition of HCl (4M) and the aqueous layer was extracted with EtOAc (3x300 mL). The organics were combined, washed with brine (2x100 mL), dried over Na_2SO_4, and evaporated to dryness to afford 8 g (33%) of 2-fluoro-6-iodobenzoic acid as a yellow solid.

Step 3: **N-Benzylprop-2-en-1-amine (Intermediate B)**



A mixture of prop-2-en-1-amine (263mL) and 1-(bromomethyl)benzene (100 g, 588.24mmol) was stirred at RT for 18 h (addition done at 0°C). The reaction mixture was then quenched by the adding 500 mL of $NaHCO_3$. The resulting aqueous solution was extracted with ether (3x500 mL) and the organics were combined, and dried over Na_2SO_4. The residue was purified by column chromatography on silica gel (eluting with a 1:100 EtOAc/PE solvent system). This resulted in 60 g (62%) of N-benzylprop-2-en-1-amine as yellow oil.

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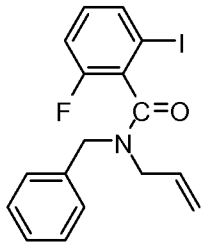
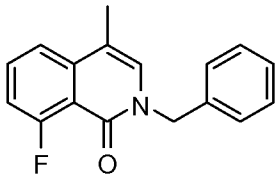
Step 4: **N-Allyl-N-benzyl-2-fluoro-6-iodobenzamide**



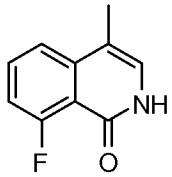
A mixture of 2-fluoro-6-iodobenzoic acid (Intermediate A, 30 g, 112.78 mmol) in $SOCl_2$ (60 mL) was heated at 80°C for 1.5 h. Excess $SOCl_2$ was removed in vacuo and the residue obtained was added to a solution of triethylamine (13.7 g, 135.64 mmol) in THF (50 mL). This solution was added dropwise to a solution of N-benzylprop-2-en-1-amine (Intermediate B,16.6 g, 112.93 mmol) in THF (150mL) cooled to 5°C. The resulting solution stirred at RT for 2 h. The mixture was concentrated and the residue was dissolved in EtOAc (200 mL). The organic layer was washed with aqueous $NaHSO_4$ (2x50 mL), aqueous $NaHCO_3$ (1x50 mL), and brine (1x50 mL), dried over Na_2SO_4, and evaporated to dryness to afford 30.0 g (67%) of N-allyl-N-benzyl-2-fluoro-6-iodobenzamide as a white solid.

Step 5: **2-Benzyl-8-fluoro-4-methylisoquinolin-1(2H)-one**



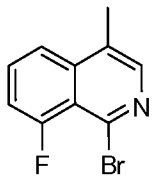
A mixture of N-allyl-N-benzyl-2-fluoro-6-iodobenzamide (198 mg, 0.50 mmol), dicyclohexylamine (362 mg, 2.00 mmol), triphenylphosphine (13.1 mg, 0.05 mmol), and $Pd(OAc)_2$ (12 mg, 0.03 mmol) in DMA (7 mL) was heated to 100°C for 18 h (reaction progress monitored by TLC (EtOAc/PE = 1:5)). The mixture was concentrated in vacuo and the residue obtained was dissolved in MeOH then added 300mg of silicon. The residue was purified by column chromatography on silica gel (eluting with 1:30 EtOAc/PE solvent system) to afford 83 mg (62%) of 2-benzyl-8-fluoro-4-methylisoquinolin-1(2H)-one as a white solid.

Step 6: **8-Fluoro-4-methylisoquinolin-1(2H)-one**



A solution of 2-benzyl-8-fluoro-4-methylisoquinolin-1(2H)-one (30 g, 112.36 mmol) in 80% H_2SO_4 (450 g) was heated to 150°C for 2.5 h. Adjustment of the pH to 9 was accomplished by the addition of NaOH (4M). The resulting aqueous solution was extracted with EtOAc (3x1000 mL). The organics were combined, washed with brine (2x500 mL), dried over Na_2SO_4, and evaporated to dryness to afford 15.8 g (79%) of 8-fluoro-4-methylisoquinolin-1(2H)-one as a white solid. LCMS: 177.0 $(M+H)^+$.

Step 7: **1-Bromo-8-fluoro-4-methylisoquinoline**



$POBr_3$ (5.68 g, 20.00 mmol) was added to a solution of 8-fluoro-4-methylisoquinolin-1(2H)-one (3.54 g, 20.00 mmol) in PBr_3 (30 mL) and the reaction mixture was heated to 120°C for 4 h (reaction progress monitored by TLC (EtOAc/PE = 1:10)). The reaction mixture was then quenched by the adding 500 mL of water/ice. Adjustment of the pH to 9 was accomplished by the addition of NaOH (4M) and the resulting aqueous solution was extracted with EtOAc (2x300 mL). The organics were combined, washed with brine (1x100 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by column chromatography on silica gel (eluting with 1:50~1:30 EA:PE solvent system). This resulted in 2.65 g (55%) of 1-bromo-8-fluoro-4-methylisoquinoline as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.94 (d, 1H), 7.89 (m, 1H), 7.61 (d, 1H), 2.55 (s, 3H). LCMS: 240 $(M+H)^+$.

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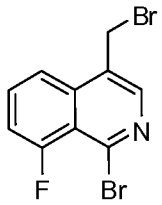
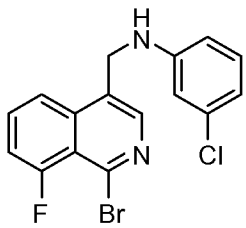
Step 8: **1-Bromo-4-(bromomethyl)-8-fluoroisoquinoline**



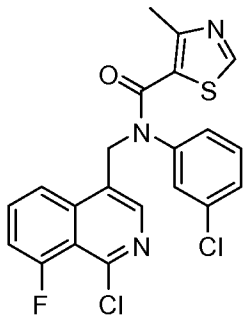
A mixture of 1-bromo-8-fluoro-4-methylisoquinoline (1.2 g, 5.02 mmol), 1-bromopyrrolidine-2,5-dione (885 mg, 5.00 mmol), and 2,2-Azobis(isobutyronitrile) (50 mg, 0.30 mmol) in CCl_4 (30 mL) was heated to 80°C for 2 h (reaction progress monitored by TLC (DCM/MeOH = 20:1)). The insolubles were removed by filtration and the filtrate was concentrated in vacuo to afford 1.7 g (crude) of 1-bromo-4-(bromomethyl)-8-fluoroisoquinoline as a yellow solid. LCMS: 318 $(M+H)^+$.

Step 9: **N-((1-Bromo-8-fluoroisoquinolin-4-yl)methyl)-3-chlorobenzenamine**



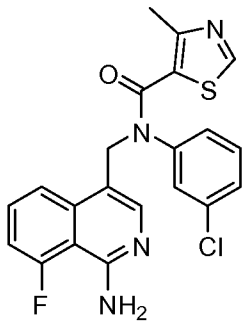
A mixture of 1-bromo-4-(bromomethyl)-8-fluoroisoquinoline (318 mg, 1.00 mmol), 3-chlorobenzenamine (255 mg, 2.01 mmol), and Na_2CO_3 (212 mg, 2.00 mmol) in DMF (20 mL) was heated to 40°C for 2 h (reaction progress monitored by TLC (EtOAc/PE = 1:5)). The reaction mixture was then quenched by the adding 60 mL of water. The resulting aqueous solution was extracted with EtOAc (2x50 mL). The organics were combined, washed with brine (1x20 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by column chromatography on silica gel (eluting with 1:30 EA/PE solvent system). This resulted in 187 mg (51%) of N-((1-bromo-8-fluoroisoquinolin-4-yl)methyl)-3-chlorobenzenamine as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.05 (m, 1H), 7.90 (d, 1H), 7.64 (d, 1H), 7.08 (m, 1H), 6.68 (s, 1H), 6.62 (d, 1H), 6.58 (d, 1H), 6.55 (d, 1H), 4.66 (s, 2H). LCMS: 365.0 $(M+H)^+$.

Step 10: **N-((1-Chloro-8-fluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)-4-methylthiazole-5-carboxamidemethylthiazole-5-carboxamide**



A mixture of N-((1-bromo-8-fluoroisoquinolin-4-yl)methyl)-3-chlorobenzenamine (350 mg, 0.95 mmol) and 4-methylthiazole-5-carbonyl chloride (700 mg, 4.30 mmol) in DMF (20 mL) was stirred at 0°C for 1 h (reaction progress monitored by TLC (PE:EA = 1:1)). Aqueous $NaHCO_3$ was added to the reaction mixture and it was extracted with EtOAc (2x50 mL). The organics were combined, dried over Na_2SO_4, and evaporated to dryness to afford 400 mg (85%) of N-((1-chloro-8-fluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)-4-methylthiazole-5-carboxamidemethylthiazole-5-carboxamide as a yellow solid. LCMS: 446.0 $(M+H)^+$.

Step 11: **N-((1-Amino-8-fluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)-4-methylthiazole-5-carboxamide**

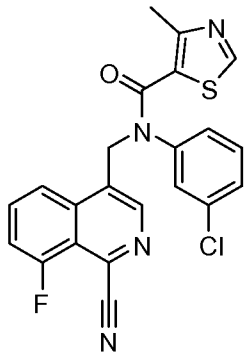


In a sealed tube, a mixture of N-((1-chloro-8-fluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)-4-methylthiazole-5-carboxamide (200 mg, 0.40 mmol), $NH_3.H_2O$ (3 mL), and $CHONH_2$(2 mL) in EtOH (2 mL) was heated to 100°C for 1 h (reaction progress monitored by TLC (PE:EA = 1:1)). The resulting solution was extracted with

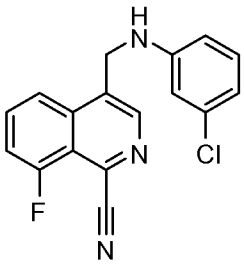
EtOAc (3x50 mL). The organics were combined, dried over Na_2SO_4, and evaporated to dryness to afford 100 mg (52%) of N-((1-amino-8-fluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)-4-methylthiazole-5-carboxamide as brown oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.86 (s, 1H), 7.99 (s, 1H), 7.95 (s, 1H), 7.79 (d, 1H), 7.51 (d, 1H), 7.20 (m, 1H), 7.14 (m, 1H), 7.12 (d, 1H), 7.01 (d, 1H), 6.79 (s, 2H), 5.31 (s, 2H), 1.98 (s, 3H). LCMS: 427.0 $(M+H)^+$.

EXAMPLE 2

N-(3-Chlorophenyl)-N-((1-cyano-8-fluoroisoquinolin-4-yl)methyl)-4-methylthiazole-5-carboxamide

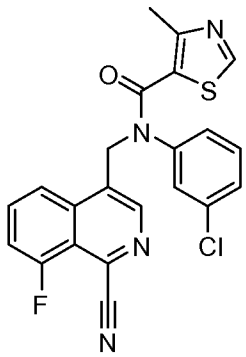


Step 1: **4-((3-Chlorophenylamino)methyl)-8-fluoroisoquinoline-1-carbonitrile**



A mixture of N-((1-bromo-8-fluoroisoquinolin-4-yl)methyl)-3-chlorobenzenamine (200 mg, 0.49 mmol), $Zn(CN)_2$ (100 mg, 0.85 mmol), and $Pd(PPh_3)_4$ (cat.) in DMF (20 mL) was heated to 80°C for 2 h. The reaction mixture was then quenched by the adding 20mL ice/water. The resulting aqueous solution was extracted with EtOAc and the organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography on silica gel (eluting with 1:5 EtOAc/PE solvent system). This resulted in 140 mg (82%) of 4-((3-chlorophenylamino)methyl)-8-fluoroisoquinoline-1-carbonitrile as a yellow solid. LCMS: 312 $(M+H)^+$.

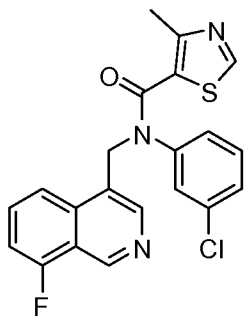
Step 2: **N-(3-Chlorophenyl)-N-((1-cyano-8-fluoroisoquinolin-4-yl)methyl)-4-methylthiazole-5-carboxamide**



N-(3-Chlorophenyl)-N-((1-cyano-8-fluoroisoquinolin-4-yl)methyl)-4-methylthiazole-5-carboxamide was synthesized as described in EXAMPLE 1, Step 10 using 4-((3-chlorophenylamino)methyl)-8-fluoroisoquinoline-1-carbonitrile and 4-methylthiazole-5-carbonyl chloride as starting materials. ^{1}HNMR (300MHz, DMSO-d_6) δ 8.91(s, 1H), 8.63 (s, 1H),8.17 (d, 1H), 8.03 (m, 1H), 7.76 (m, 1H), 7.49 (s, 1H), 7.27 (d, 1H), 7.19 (t, 1H), 6.98 (d, 1H), 5.69 (s, 2H), 2.45 (s, 3H). LCMS: 437.0 $(M+H)^+$.

EXAMPLE 3

N-(3-Chlorophenyl)-N-((8-fluoroisoquinolin-4-yl)methyl)-4-methylthiazole-5-carboxamide



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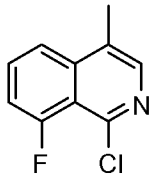
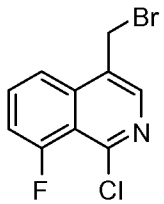
Step 1: **1-Chloro-8-fluoro-4-methylisoquinoline**



A mixture of 8-fluoro-4-methylisoquinolin-1(2H)-one (3 g, 16.95 mmol) in $POCl_3$ (40 mL) was heated to 80°C for 2 h. The mixture was concentrated and the residue was partitioned between EtOAc/water (1:1, 100 mL). Adjustment of the pH to 8 was accomplished by the addition of $NH_3.H_2O$ (25%). The two layers were separated and the aqueous layer was extracted with EtOAc (1x50 mL). The organics were combined, dried over Na_2SO_4, and evaporated to dryness to afford 3.3 g (99%) of 1-chloro-8-fluoro-4-methylisoquinoline as a white solid. LCMS: 196 $(M+H)^+$.

Step 2: **4-(Bromomethyl)-1-chloro-8-fluoroisoquinoline**



4-(Bromomethyl)-1-chloro-8-fluoroisoquinoline was synthesized as described in EXAMPLE 1, Step 8 using 1-chloro-8-fluoro-4-methylisoquinoline as starting material. LCMS: 274 $(M+H)^+$.

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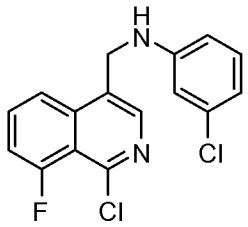
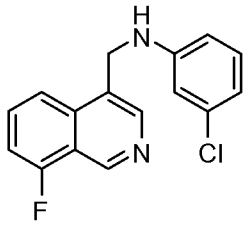
Step 3: **3-Chloro-N-((1-chloro-8-fluoroisoquinolin-4-yl)methyl)benzenamine**



3-Chloro-N-((1-chloro-8-fluoroisoquinolin-4-yl)methyl)benzenamine was synthesized as described in EXAMPLE 1, Step 9 using 1-chloro-8-fluoro-4-methylisoquinoline and 3-chloroaniline as starting materials. LCMS: 321.0 $(M+H)^+$.

Step 4: **3-Chloro-N-((8-fluoroisoquinolin-4-yl)methyl)benzenamine**



A solution of 3-chloro-N-((1-chloro-8-fluoroisoquinolin-4-yl)methyl)benzenamine (500 mg, 1.56 mmol) and Pd/C (100 mg) in MeOH (20 mL) was hydrogenated (with a balloon of hydrogen) for 4 h at RT. A filtration was performed to remove the Pd/C and the filtrate was evaporated to dryness. The residue was dissolved in 30 mL of EtOAc and the organic layer was washed with $NaHCO_3$ (2x20 mL) and brine (2x20 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness to afford 380 mg (85%) of 3-chloro-N-((8-fluoroisoquinolin-4-yl)methyl)benzenamine as a yellow solid. LCMS: 286 $(M+H)^+$.

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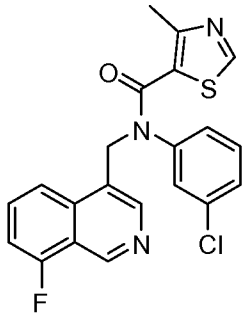
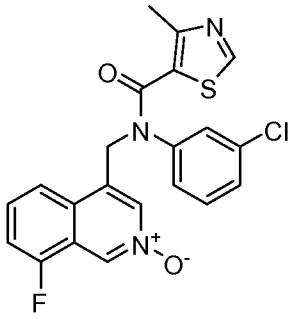
Step 5: **N-(3-Chlorophenyl)-N-((8-fluoroisoquinolin-4-yl)methyl)-4-methylthiazole-5-carboxamide**



A solution of 4-methylthiazole-5-carboxylic acid (526 mg, 3.68 mmol) in $SOCl_2$ (10 mL) was heated to 80°C for 2 h. The excess $SOCl_2$ was removed and the residue was dissolved in DCM (5 mL). This was followed by the addition of a solution of 3-chloro-N-((8-fluoroisoquinolin-4-yl)methyl)benzenamine (350 mg, 1.22 mmol) in DCM (3 mL) dropwise. The resulting solution was stirred at RT for 1 h. The resulting solution was diluted with 30 mL of DCM and was washed with $NaHCO_3$ (2x20 mL) and brine (2x20 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography on silica gel (eluting with 1:10 EtOAc/PE solvent system) to afford in 210 mg (42%) of N-(3-chlorophenyl)-N-((8-fluoroisoquinolin-4-yl)methyl)-4-methylthiazole-5-carboxamide as yellow oil. ^{1}HNMR (300MHz, DMSO-d_6) δ 9.38(s, 1H), 8.90 (s, 1H), 8.39 (s, 1H), 8.05 (d, 1H), 7.91 (m, 1H), 7.53 (t, 1H), 7.34 (s, 1H), 7.23 (d, 1H), 7.13 (t, 1H), 6.82 (d, 1H), 5.61(s, 2H), 2.44 (s, 3H). LCMS: 412.0 $(M+H)^+$.

EXAMPLE 4

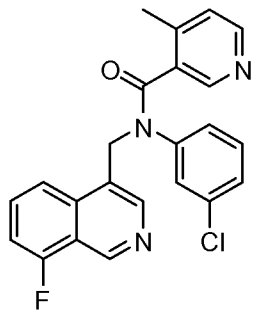
4-((N-(3-Chlorophenyl)-4-methylthiazole-5-carboxamido)methyl)-8-fluoroisoquinoline 2-oxide



A mixture of N-(3-chlorophenyl)-N-((8-fluoroisoquinolin-4-yl)methyl)-4-methylthiazole-5-carboxamide (100 mg, 0.24 mmol) and *m*-CPBA (125.5 g, 729.65 mmol) in DCM (10 mL) was stirred at RT for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (eluting with 75:1 DCM/MeOH solvent system) to afford 50 mg (48%) of 4-((N-(3-chlorophenyl)-4-methylthiazole-5-carboxamido)methyl)-8-fluoroisoquinoline 2-oxide as an off-white solid. ^{1}HNMR 400MHz, DMSO-d_6) δ 8.91(s, 1H), 8.77 (s, 1H), 8.10 (s, 1H), 7.93 (d, 1H), 7.71 (m, 1H), 7.54 (t, 1H), 7.44 (s, 1H), 7.32 (d, 1H), 7.21 (t, 1H), 6.92 (d, 1H), 5.54 (s, 2H), 2.44 (s, 3H). LCMS: 428 $(M+H)^+$.

EXAMPLE 5

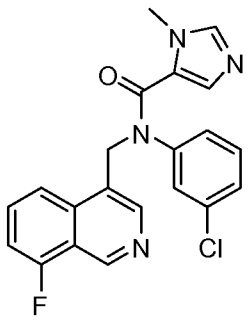
N-(3-Chlorophenyl)-N-((8-fluoroisoquinolin-4-yl)methyl)-4-methylnicotinamide



N-(3-Chlorophenyl)-N-((8-fluoroisoquinolin-4-yl)methyl)-4-methylnicotinamide was synthesized as described in EXAMPLE 3 using 3-chloro-N-((8-fluoroisoquinolin-4-yl)methyl)benzenamine and 4-methylnicotinic acid as starting materials. ^{1}HNMR (400MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.78 (s, 1H), 8.49 (s, 2H), 8.10-8.01 (m, 2H), 7.64 (m, 2H), 7.43 (s, 1H), 7.13-6.99 (m, 2H), 6.80 (d, 1H), 5.64 (s, 2H), 2.43 (s, 3H). LCMS: 406 $(M+H)^+$.

EXAMPLE 6

N-(3-Chlorophenyl)-N-((8-fluoroisoquinolin-4-yl)methyl)-1-methyl-1H-imidazole-5-carboxamide



N-(3-Chlorophenyl)-N-((8-fluoroisoquinolin-4-yl)methyl)-1-methyl-1H-imidazole-5-carboxamide was synthesized as described in EXAMPLE 3 using 3-chloro-N-((8-fluoroisoquinolin-4-yl)methyl)benzenamine and 1-methyl-1H-imidazole-5-carboxylic acid as starting materials. ^{1}HNMR (400MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.22 (s, 1H), 7.94 (m, 2H), 7.67-7.62 (m, 1H), 7.25-7.19 (m, 2H), 7.10 (m, 1H), 6.92 (m, 1H), 6.67 (m, 1H), 6.05 (s, 1H), 5.43 (s, 2H), 3.93 (s, 3H).. LCMS: 395 $(M+H)^+$.

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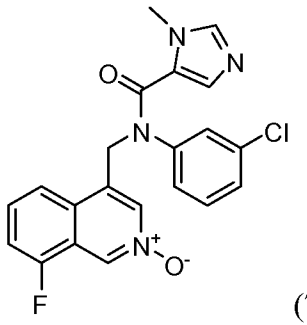
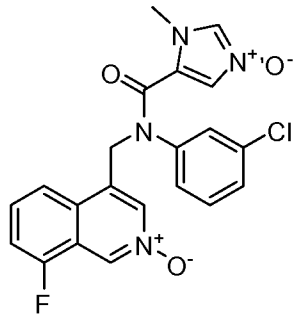
EXAMPLE 7 and EXAMPLE 8

4-((N-(3-Chlorophenyl)-1-methyl-1H-imidazole-5-carboxamido)methyl)-8-fluoroisoquinoline 2-oxide and **4-((N-(3-Chlorophenyl)-1-methyl-3-oxido-1H-imidazole-5-carboxamido)methyl)-8-fluoroisoquinoline 2-oxide**



(7) and



(8)

4-((N-(3-Chlorophenyl)-1-methyl-1H-imidazole-5-carboxamido)methyl)-8-fluoroisoquinoline 2-oxide and 4-((N-(3-chlorophenyl)-1-methyl-3-oxido-1H-imidazole-5-carboxamido)methyl)-8-fluoroisoquinoline 2-oxide were synthesized as described in EXAMPLE 4 using N-(3-chlorophenyl)-N-((8-fluoroisoquinolin-4-yl)methyl)-1-methyl-1H-imidazole-5-carboxamide as a starting material. The 2 compounds were separated by reverse phase chromatography.

Mono N-Oxide: ^{1}HNMR (400MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.51 (d, 2H), 7.76 (m, 2H), 7.46-7.41 (m, 2H), 7.33 (t, 1H), 7.23 (s, 1H), 7.04 (s, 1H), 6.32 (s, 1H), 5.48 (s, 2H), 4.12 (s, 3H). LCMS: 410 $(M)^+$.

Di N-Oxide: ^{1}HNMR (400MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 7.73 (m, 2H), 7.46-7.40 (m, 2H), 7.35 (t, 1H), 7.23 (t, 1H), 7.02 (d, 1H), 6.36 (s, 1H), 5.45 (s, 2H), 4.10 (s, 3H). LCMS: 427 $(M+H)^+$.

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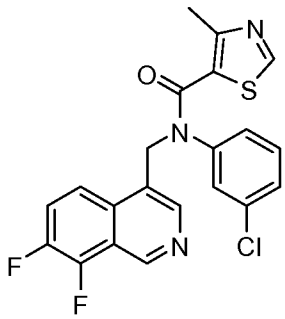
EXAMPLE 9

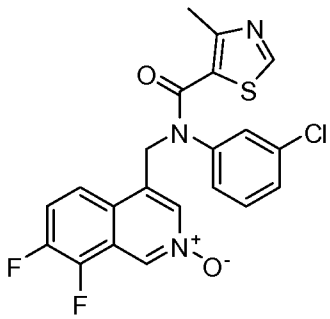
N-(3-Chlorophenyl)-N-((7,8-difluoroisoquinolin-4-yl)methyl)-4-methylthiazole-5-carboxamide



N-(3-Chlorophenyl)-N-((7,8-difluoroisoquinolin-4-yl)methyl)-4-methylthiazole-5-carboxamide was synthesized as described in EXAMPLE 3 using 3,4-difluoroaniline as a starting material. ^{1}HNMR (300MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.87 (s, 1H), 8.25 (s, 1H), 8.15 (s, 1H), 8.12 (d, 1H), 7.38 (d, 1H), 7.26 (m, 1H), 7.16 (m, 1H), 6.82 (s, 1H), 5.61 (s, 2H), 2.44 (s, 3H). LCMS: 430 $(M+H)^+$.

EXAMPLE 10

4-((N-(3-Chlorophenyl)-4-methylthiazole-5-carboxamido)methyl)-7,8-difluoroisoquinoline 2-oxide



4-((N-(3-Chlorophenyl)-4-methylthiazole-5-carboxamido)methyl)-7,8-difluoroisoquinoline 2-oxide was synthesized as described in EXAMPLE 4 using N-(3-chlorophenyl)-N-((7,8-difluoroisoquinolin-4-yl)methyl)-4-methylthiazole-5-carboxamide as a starting material. ^{1}HNMR (400MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.82 (s, 1H), 8.06 (s, 1H), 7.97 (m, 1H), 7.84 (m, 1H), 7.45 (m, 1H), 7.29 (m, 1H), 7.21 (t, 1H), 6.91 (d, 1H), 5.51 (s, 2H), 2.42 (s, 3H).

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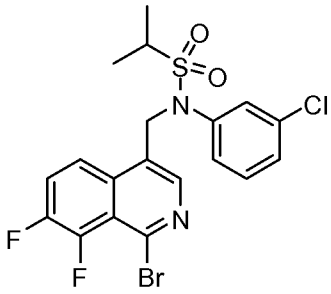
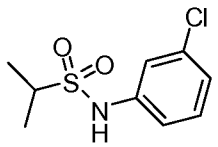
EXAMPLE 11

N-((1-Bromo-7,8-difluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)propane-2-sulfonamide



Step 1: **N-(3-Chlorophenyl)propane-2-sulfonamide**



A mixture of 3-chloroaniline (537 mg, 4.23 mmol), propane-2-sulfonyl chloride (500 mg, 3.52 mmol) and triethylamine (1.73 mL, 12.6 mmol) in DCM (20 mL) was stirred at RT for 18 h (addition of triethylamine was done at 0°C). The reaction mixture was then quenched by the adding 500 mL of $NaHCO_3$. The organics were combined, dried over Na_2SO_4, and the residue was purified by column chromatography on silica gel (eluting with a 1:10 EtOAc/Hexanes solvent system). This resulted in 410mg (50%) of N-(3-chlorophenyl)propane-2-sulfonamide as white solid. ^{1}HNMR (400MHz, MeOH-d_4) δ 7.30-7.27 (m, 2H), 7.18-7.14 (m, 1H), 7.10-7.06 (m, 1H), 3.31-3.22 (m, 1H), 1.32 (d, 6H). LCMS: 234. $(M+H)^+$.

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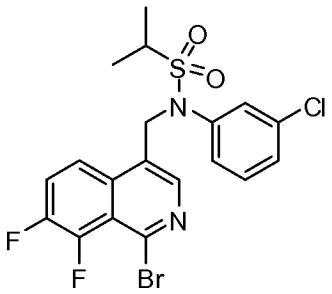
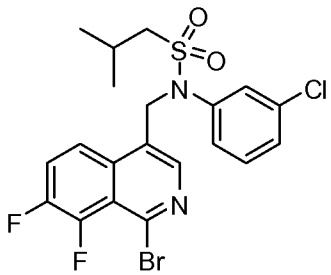
Step 2: **N-((1-Bromo-7,8-difluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)propane-2-sulfonamide**



A mixture of N-(3-chlorophenyl)propane-2-sulfonamide (209 mg, 0.733 mmol), 1-bromo-4-(bromomethyl)-7,8-difluoroisoquinoline (200 mg, 0.733 mmol) and potassium carbonate (303 mg, 2.19 mmol) in ACN (5 mL) was stirred at RT for 18 h. The residue was purified by column chromatography on silica gel (eluting with 3:7 EtOAc/Hexanes solvent system) to afford 175 mg (60%) of N-((1-bromo-7,8-difluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)propane-2-sulfonamide as an clear oil. ^{1}HNMR (400MHz, DMSO-d_6) δ 8.33-8.28 (m, 1H), 8.22-8.14 (m, 1H), 8.12 (s, 1H), 7.51 (s, 1H), 7.32-7.21 (m, 3H), 5.50 (s, 2H), 3.51 (sept, 1H), 1.33 (d, 6H). LCMS: 489. $(M+H)^+$.

EXAMPLE 12

N-((1-Bromo-7,8-difluoroisoquinolin-4yl)methyl)-N-(3-chlorophenyl)-2-methylpropane-1-sulfonamide

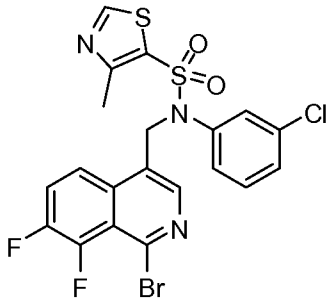


N-((1-Bromo-7,8-difluoroisoquinolin-4yl)methyl)-N-(3-chlorophenyl)-2-methylpropane-1-sulfonamide was synthesized as described in EXAMPLE 11 using 2-methylpropane-1-sulfonyl chloride as a starting material in step 1 and N-(3-chlorophenyl)-2-methylpropane-1-sulfonamide as a starting material in step 2. ^{1}HNMR (400MHz, DMSO-d_6) δ 8.31-8.25 (m, 1H), 8.22-8.15 (m, 1H), 8.11 (s, 1H),

7.46 (s, 1H), 7.30-7.26 (m, 3H), 5.48 (s, 2H), 3.23 (d, 2H), 2.19 (sept, 1H), 1.04 (d, 6H). LCMS: 504. $(M+H)^+$.

EXAMPLE 13

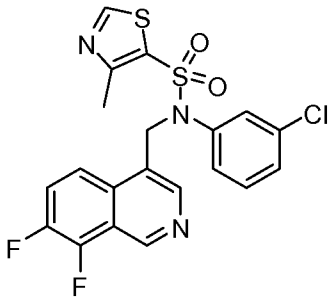
N-((1-bromo-7,8-difluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)-4-methylthiazole-5-sulfonamide



N-((1-Bromo-7,8-difluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)-4-methylthiazole-5-sulfonamide was synthesized as described in EXAMPLE 11 using 4-methylthiazole-5-sulfonyl chloride as a starting material in step 1 and N-(3-chlorophenyl)-4-methylthiazole-5-sulfonamide as a starting material in step 2. ^{1}HNMR (400MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.31-8.21 (m, 2H), 8.11 (s, 1H), 7.35 (m, 1H), 7.29-7.20 (m, 2H), 7.07-7.04 (m, 1H), 5.30 (s, 2H), 2.26 (s, 3H). LCMS: 544. $(M+H)^+$.

EXAMPLE 14

N-(3-chlorophenyl)-N-((7,8-difluoroisoquinolin-4-yl)methyl)-4-methylthiazole-5-sulfonamide

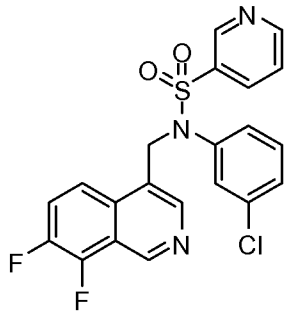


A solution of N-((1-bromo-7,8-difluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)-4-methylthiazole-5-sulfonamide (110 mg, 0.205 mmol) and Pd/C (100 mg) in MeOH (20 mL) was hydrogenated (with a balloon of hydrogen) for 8 h at RT. A filtration was

performed to remove the Pd/C and the filtrate was evaporated to dryness. The mixture was purified by reverse phase column chromatography (eluting with 0%-100% acetonitrile/0.05%trifluoroacetic acid in H_2O solvent system) to afford 9.4 mg (10%) of N-(3-chlorophenyl)-N-((7,8-difluoroisoquinolin-4-yl)methyl)-4-methylthiazole-5-sulfonamide as a solid. ^{1}HNMR (400MHz, DMSO-d_6) δ 9.47 (s, 1H), 9.22 (s, 1H), 8.44-8.40 (m, 1H), 8.29 (s, 1H), 8.10-8.00 (m, 1H), 7.29-7.27 (m, 1H), 7.24-7.20 (m, 1H), 7.13-7.11 (m, 1H), 7.08-7.00 (m, 1H), 5.39 (s, 2H), 2.28 (s, 3H). LCMS: 465. $(M+H)^+$.

EXAMPLE 15

N-(3-chlorophenyl)-N-((7,8-difluoroisoquinolin-4-yl)methyl)pyridine-3-sulfonamide



N-(3-Chlorophenyl)-N-((7,8-difluoroisoquinolin-4-yl)methyl)pyridine-3-sulfonamide was synthesized as described in EXAMPLES 11 and 14 using N-(3-chlorophenyl)pyridine-3-sulfonamide and 1-bromo-4-(bromomethyl)-7,8-difluoroisoquinoline as starting materials. ^{1}HNMR (400MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.96 (dd, 1H), 8.85 (d, 1H), 8.34 (s, 1H), 8.31-8.27 (m, 1H), 8.17-8.10 (m, 1H), 8.09-8.06 (m, 1H), 7.72 (m, 1H), 7.30-7.27 (m, 1H), 7.22 (t, 1H), 7.13 (t, 1H), 7.00-6.97 (m, 1H), 5.33 (s, 2H). LCMS: 447.6 $(M+H)^+$.

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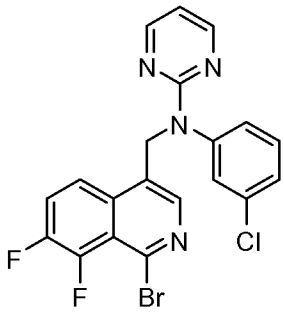
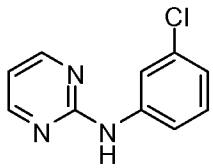
EXAMPLE 16

N-((1-Bromo-7,8-difluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)pyrimidin-2-amine



Step 1: **N-(3-Chlorophenyl)pyrimidin-2-amine**



A mixture of 2-chloropyrimidine (4 g, 35 mmol) and 3-chloroaniline (4.4 g, 35 mmol) was heated to 200°C for 15 min in a microwave. The cooled reaction mixture was partitioned between EtOAc and HCl (1 M). The organic layer was washed with HCl (1 M, 3x), brine (2x), dried, and evaporated to dryness. The residue was purified by flash chromatography on silica gel (eluting with 0 to 50% EtOAc/Hexanes) to afford 4 g of N-(3-chlorophenyl)pyrimidin-2-amine as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, 2H), 7.86 (t, 1H), 7.54 (s, 1H), 7.39 (d, 1H), 7.25 (d, 1H), 7.01 (d, 1H), 6.77 (t, 1H).

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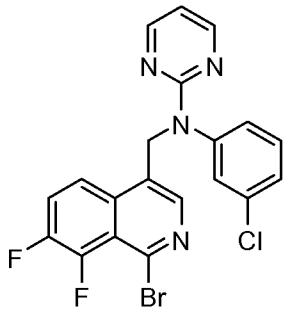
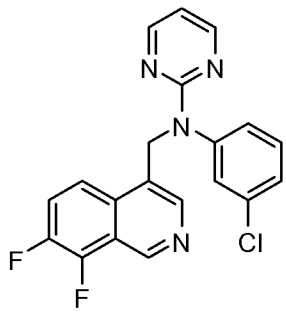
Step 2: **N-((1-Bromo-7,8-difluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)pyrimidin-2-amine**



Sodium hydride (150 mg, 3.75 mmol, 1.6 equiv) was added to a solution of N-(3-chlorophenyl)pyrimidin-2-amine (500 mg, 2.4 mmol) in DMF (20 mL) and stirred for 15 min at 0 °C (ice bath). Solid 1-bromo-4-(bromomethyl)-7,8-difluoroisoquinoline (815 mg, 2.41 mmol) was added to the reaction mixture and the resulting solution was stirred for an additional 10 min at 0 °C, warmed to RT and stirred for an additional 1h. The crude reaction mixture was poured into H_2O and extracted with EtOAc and dichloromethane. The organic layer was dried (Na_2SO_4), filtered, and concentrated to afford N-((1-bromo-7,8-difluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)pyrimidin-2-amine. ^{1}HNMR (400MHz, DMSO-d_6) δ 8.44 (d, 2H), 8.16-8.05 (m, 3H), 7.50-7.48 (m, 1H), 7.32-7.20 (m, 3H), 6.87 (t, 1H), 5.69 (s, 2H). LCMS: 462.9 $(M+H)^+$.

EXAMPLE 17

N-(3-Chlorophenyl)-N-((7,8-difluoroisoquinolin-4-yl)methyl)pyrimidin-2-amine

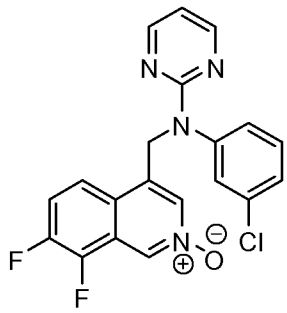


N-(3-chlorophenyl)-N-((7,8-difluoroisoquinolin-4-yl)methyl)pyrimidin-2-amine was synthesized as described in EXAMPLE 14 using N-((1-bromo-7,8-difluoroisoquinolin-4-yl)methyl)-N-(3-chlorophenyl)pyrimidin-2-amine as the starting material. ^{1}HNMR

(400MHz, CD_3OD) δ 9.35 (s, 1H), 8.40 (d, 2H), 8.31 (s, 1H), 8.09 (dd, 1H), 7.80-7.73 (m, 1H), 7.28-7.17 (m, 3H), 7.08-7.07 (m, 1H), 6.82 (t, 1H), 5.77 (s, 2H). LCMS: 383.1 $(M+H)^+$.

EXAMPLE 18

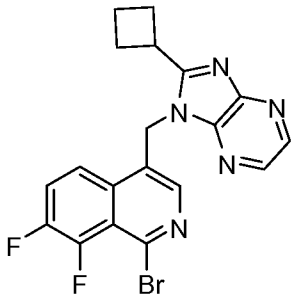
4-(((3-Chlorophenyl)(pyrimidin-2-yl)amino)methyl)-7,8-difluoroisoquinoline 2-oxide



4-(((3-Chlorophenyl)(pyrimidin-2-yl)amino)methyl)-7,8-difluoroisoquinoline 2-oxide was synthesized as described in EXAMPLE 4 using 4-(((3-chlorophenyl)(pyrimidin-2-yl)amino)methyl)-7,8-difluoroisoquinoline as the starting material. ^{1}HNMR (400MHz, CD_3OD) δ 8.99 (s, 1H), 8.41 (d, 2H), 8.11 (s, 1H), 8.03 (dd, 1H), 7.74-7.67 (m, 1H), 7.42-7.34 (m, 2H), 7.28-7.23 (m, 2H), 6.86 (t, 1H), 5.74 (s, 2H). LCMS: 399.1 $(M+H)^+$.

EXAMPLE 19

1-Bromo-4-((2-cyclobutyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-7,8-difluoroisoquinoline



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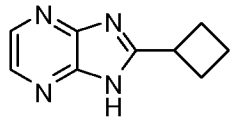
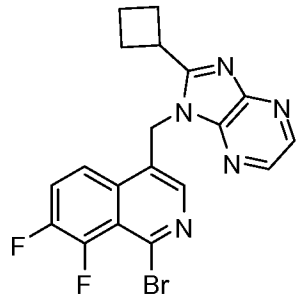
Step 1: **2-Cyclobutyl-1H-imidazo[4,5-b]pyrazine**



To PPA (35 mL) stirred at 120°C was added pyrazine-2,3-diamine (8 g, 73 mmol) followed by cyclobutanecarboxylic acid (7.3 mL, 77 mmol). The resulting mixture was heated for 4 h at 160°C and it was then allowed to cool to 80°C. A solution of NaOH (35 g in 250 mL of H_2O) was then added and the resulting precipitate was collected by filtration and dried to give 10g of 2-cyclobutyl-1H-imidazo[4,5-b]pyrazine as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 2H), 3.76 (m, 1H), 2.44-2.30 (m, 4H), 2.06 (m, 1H), 1.56 (m, 1H).

Step 2: **1-Bromo-4-((2-cyclobutyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-7,8-difluoroisoquinoline**



1-Bromo-4-((2-cyclobutyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-7,8-difluoroisoquinoline was synthesized as described in EXAMPLE 16, Step 2 using 2-cyclobutyl-1H-imidazo[4,5-b]pyrazine and 1-bromo-4-(bromomethyl)-7,8-difluoroisoquinoline as starting materials. ^{1}HNMR (400MHz, DMSO-d_6) δ 8.48 (d, 1H), 8.29 (d, 1H), 8.22-8.11 (m, 2H), 7.63 (s, 1H), 5.92 (s, 2H), 3.93 (m, 1H), 2.45-2.35 (m, 2H), 2.20-2.10 (m, 2H), 2.02-1.83 (m, 2H). LCMS: 432.0 $(M+H)^+$.

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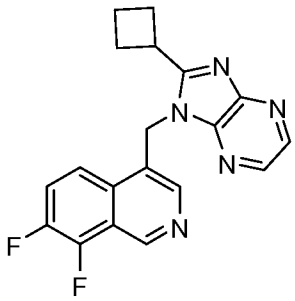
EXAMPLE 20

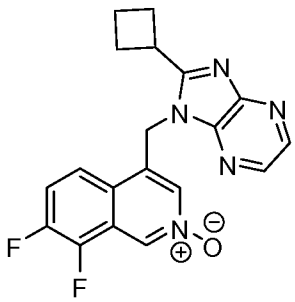
4-((2-Cyclobutyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-7,8-difluoroisoquinoline



4-((2-Cyclobutyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-7,8-difluoroisoquinoline was synthesized as described in EXAMPLE 14 using 1-bromo-4-((2-cyclobutyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-7,8-difluoroisoquinoline as the starting material. ^{1}HNMR (400MHz, CD_3OD) δ 9.61 (br s, 1H), 8.52 (d, 1H), 8.36 (d, 1H), 8.26-8.24 (m, 1H), 8.03-7.98 (m, 2H), 6.10 (s, 2H), 3.99 (m, 1H), 2.57-2.47 (m, 2H), 2.30-2.22 (m, 2H), 2.15-1.94 (m, 2H). LCMS: 352.2 $(M+H)^+$.

EXAMPLE 21

4-((2-cyclobutyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-7,8-difluoroisoquinoline 2-oxide



4-((2-Cyclobutyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-7,8-difluoroisoquinoline 2-oxide was synthesized as described in EXAMPLE 4 using 4-((2-cyclobutyl-1H-imidazo[4,5-b]pyrazin-1-yl)methyl)-7,8-difluoroisoquinoline as the starting material. ^{1}HNMR (400MHz, CD_3OD) δ 9.04 (s, 1H), 8.51 (d, 1H), 8.34 (d, 1H), 8.15 (dd, 1H), 7.84-7.77 (m, 1H), 7.54 (s, 1H), 6.02 (s, 2H), 4.00 (m, 1H), 2.62-2.52 (m, 2H), 2.38-2.31 (m, 2H), 2.19-1.96 (m, 2H). LCMS: 368.1 $(M+H)^+$.

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[0179] The following compounds can generally be made using the methods described above, and are represented herein using the Simplified Molecular Input Line Entry System, or SMILES. SMILES is a modern chemical notation system, developed by David Weininger and Daylight Chemical Information Systems, Inc., that is built into all major commercial chemical structure drawing software packages. Software is not needed to interpret SMILES text strings, and an explanation of how to translate SMILES into structures can be found in Weininger, D., *J. Chem. Inf. Comput. Sci.* 1988, *28*, 31-36. All SMILES strings used herein, as well as many IUPAC names, were generated using CambridgeSoft's ChemDraw 10.0. It is expected that these compounds when made will have activity similar to those that have been made in the examples above.

FC1=C(C=NC=C2CN(C3=CC=CC=N3)C4=CC(Cl)=CC=C4)C2=CC=C1F

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FC1=C(C=NC=C2CN(C3=CC=NC=C3)C4=CC(Cl)=CC=C4)C2=CC=C1F

FC1=C(C=NC=C2CN(C3=CC=NC=N3)C4=CC(Cl)=CC=C4)C2=CC=C1F

FC1=C(C=NC=C2CN(C3=CN=CC=N3)C4=CC(Cl)=CC=C4)C2=CC=C1F

FC1=C(C=NC=C2CN(C3=CC=CN=N3)C4=CC(Cl)=CC=C4)C2=CC=C1F

FC1=C(C=NC=C2CN(C3=CC=NN=C3)C4=CC(Cl)=CC=C4)C2=CC=C1F

FC1=C(C=NC=C2CN(C3=CN=CN=C3)C4=CC(Cl)=CC=C4)C2=CC=C1F

FC1=C(C=[N+]([O-])C=C2CN(C3=CC=CC=N3)C4=CC(Cl)=CC=C4)C2=CC=C1F

FC1=C(C=[N+]([O-])C=C2CN(C3=CC=CN=C3)C4=CC(Cl)=CC=C4)C2=CC=C1F

FC1=C(C=[N+]([O-])C=C2CN(C3=CC=NC=C3)C4=CC(Cl)=CC=C4)C2=CC=C1F

FC1=C(C=[N+]([O-])C=C2CN(C3=CC=NC=N3)C4=CC(Cl)=CC=C4)C2=CC=C1F

FC1=C(C=[N+]([O-])C=C2CN(C3=CN=CC=N3)C4=CC(Cl)=CC=C4)C2=CC=C1F

FC1=C(C=[N+]([O-])C=C2CN(C3=CC=CN=N3)C4=CC(Cl)=CC=C4)C2=CC=C1F

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C2=CC=C1F

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FC1=C(C=[N+]([O-])C=C2CN3C(N=CC=N4)=C4N=C3CC(C)C)C2=CC=C1F

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FC1=C(C=[N+]([O-])C=C2CN3C(N=CC=N4)=C4N=C3C5CC(F)(F)C5)C2=CC=C1F

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C2=CC=C1F

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C2=CC=C1F

FC1=C(C=[N+]([O-])C=C2CN3C(N=CC=N4)=C4N=C3CC5CCC5)C2=CC=C1F

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C2=CC=C1F

FC1=C(C=NC=C2CN3C(N=CC=C4C)=C4N=C3C5CCC5)C2=CC=C1F

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FC1=C(C=[N+]([O-])C=C2CN3C(N=CC=C4C)=C4N=C3C5CC(F)(F)C5)
C2=CC=C1F

FC1=C(C=[N+]([O-])C=C2CN3C(N=CC=C4C)=C4N=C3C5=CC=NC=C5C)
C2=CC=C1F

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FC1=C(C=[N+]([O-])C=C2CN3C(N=CC=C4C)=C4N=C3C5=CC=CC=C5C)
C2=CC=C1F

FC1=C(C=[N+]([O-])C=C2CN3C(N=CC=C4C)=C4N=C3CC5CCC5)C2=CC=C1F

FC1=C(C=[N+]([O-])C=C2CN3C(N=CC=C4C)=C4N=C3CC5=CC=CC=C5)
C2=CC=C1F

[0180] The activity of the compounds in Examples 1-21 as iNOS inhibitors is illustrated in the following assay. The other compounds listed above, which have not yet been made and/or tested, are predicted to have activity in this assay as well.

Biological Activity Assay

[0181] Enzyme Source. The source of nitric oxide synthase (NOS) enzyme can be generated in several ways including induction of endogenous iNOS using cytokines and/or lipopolysaccharide (LPS) in various cell types known in the art. Alternatively, the gene encoding the enzyme can be cloned and the enzyme can be generated in cells via heterologous expression from a transient or stable expression plasmid with suitable features for protein expression as are known in the art. Enzymatic activity (nitric oxide production) is calcium independent for iNOS, while the constitutive NOS isoforms, nNOS and eNOS, become active with the addition of various cofactors added to cellular media or extract as are well known in the art. Enzymes specified in Table 1 were expressed in HEK293 cells transiently transfected with human iNOS. Those of skill in the art will easily be able to set upsimilar assays for eNOS and nNOS in order to determine selectivity.

[0182] DAN Assay. A major metabolic pathway for nitric oxide is to nitrate and nitrite, which are stable metabolites within tissue culture, tissue, plasma, and urine (S Moncada, A Higgs, N Eng J Med 329, 2002 (1993)). Tracer studies in humans have demonstrated that perhaps 50% of the total body nitrate/nitrite originates from the substrate for NO synthesis, L-arginine (PM Rhodes, AM Leone, PL Francis, AD Struthers, S Moncada, Biomed Biophys Res. Commun. 209, 590 (1995); L. Castillo et al., Proc Natl Acad Sci USA 90, 193 (1993). Although nitrate and nitrite are not

measures of biologically active NO, plasma and urine samples obtained from subjects after a suitable period of fasting, and optionally after administration of a controlled diet (low nitrate/low arginine), allow the use of nitrate and nitrite as an index of NO activity (C Baylis, P Vallance, Curr Opin Nephrol Hypertens 7, 59 (1998)).

[0183] The level of nitrate or nitrite in the specimen can be quantified by any method known in the art which provides adequate sensitivity and reproducibility. A variety of protocols have also been described for detecting and quantifying nitrite and nitrate levels in biological fluids by ion chromatography (e.g., SA Everett et al., J. Chromatogr. 706, 437 (1995); JM Monaghan et al., J. Chromatogr. 770, 143 (1997)), high-performance liquid chromatography (e.g., M Kelm et al., Cardiovasc. Res. 41, 765 (1999)), and capillary electrophoresis (MA Friedberg et al., J. Chromatogr. 781, 491 (1997)). For example, 2,3-diaminonaphthalene reacts with the nitrosonium cation that forms spontaneously from NO to form the fluorescent product 1*H*-naphthotriazole. Using 2,3-diaminonaphthalene ("DAN"), researchers have developed a rapid, quantitative fluorometric assay that can detect from 10 nM to 10 μM nitrite and is compatible with a multi-well microplate format. DAN is a highly selective photometric and fluorometric reagent for Se and nitrite ion. DAN reacts with nitrite ion and gives fluorescent naphthotriazole (MC Carré et al., Analusis 27, 835-838 (1999)). Table 1 provides the test results of various compounds disclosed herein using the DAN assay.

[0184] A specimen can be processed prior to determination of nitrate or nitrite as required by the quantification method, or in order to improve the results, or for the convenience of the investigator. For example, processing can involve centrifuging, filtering, or homogenizing the sample. If the sample is whole blood, the blood can be centrifuged to remove cells and the nitrate or nitrite assay performed on the plasma or serum fraction. If the sample is tissue, the tissue can be dispersed or homogenized by any method known in the art prior to determination of nitrate or nitrite. It may be preferable to remove cells and other debris by centrifugation or another method and to determine the nitrate or nitrite level using only the fluid portion of the sample, or the extracellular fluid fraction of the sample. The sample can also be preserved for later determination, for example by freezing of urine or plasma samples. When appropriate,

additives may be introduced into the specimen to preserve or improve its characteristics for use in the nitrate or nitrite assay.

[0185] The "level" of nitrate, nitrite, or other NO-related product usually refers to the concentration (in moles per liter, micromoles per liter, or other suitable units) of nitrate or nitrite in the specimen, or in the fluid portion of the specimen. However, other units of measure can also be used to express the level of nitrate or nitrite. For example, an absolute amount (in micrograms, milligrams, nanomoles, moles, or other suitable units) can be used, particularly if the amount refers back to a constant amount (e.g., grams, kilograms, milliliters, liters, or other suitable units) of the specimens under consideration. A number of commercially available kits can be used. Results are shown below in Table 1.

Table 1.

EXAMPLE	**hiNOS EC50** **+ indicates ≤ 5 µM** **- indicates > 5 µM** **ND indicates No Data**
1	+
2	+
3	+
4	+
5	+
6	+
7	+
8	-
9	+
10	+
11	ND
12	ND
13	ND
14	-

15	-
16	ND
17	-
18	-
19	-
20	-
21	-

[0186] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

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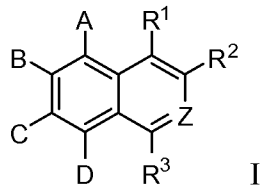
CLAIMS

What is claimed is:

1. A compound of structural Formula I:



I

or a salt, ester, or prodrug thereof, wherein:

Z is selected from the group consisting of N and N^+–O^-;

R^1 is selected from the group consisting of acyl, alkyl, alkylene, aminoalkyl, amidoalkyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkyl, arylalkoxy, arylamino, arylthio, carboxy, cycloalkyl, ester, ether, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylamino, heterocycloalkyl, heterocycloalkylalkyl, hydrazinyl, hydrogen, imino, thio, sulfonate, sulfonylamino and sulfonylaminoalkyl, any of which may be optionally substituted;

R^2 is selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkyl, alkylene, alkylamino, alkynyl, alkylimino, amido, amino, aryl, carboxy, cyano, cycloalkyl, ester, halo, haloalkyl, heteoaryl, heterocycloalkyl and hydrogen, any of which may be optionally substituted; or, alternatively, R^2 may combine with R^1 to form heterocycloalkyl, which may be optionally substituted;

R^3 is selected from the group consisting of acyl, alkoxy, alkyl, amino, halo, haloalkyl, cyano, and hydrogen, any of which may be optionally substituted; and

A, B, C and D are each independently selected from the group consisting of acyl, alkoxy, alkyl, alkylene, alkylamino, alkynyl, amido, amino, aminosulfonyl, aryl, arylalkoxy, arylamino, arylthio, carboxy, cycloalkyl, ester, ether, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylamino, heterocycloalkyl, hydrazinyl, hydrogen, imino, thio, sulfonate and sulfonylamino, any of which may be optionally substituted; or, alternatively, any two or more A, B, C and D may combine to form aryl, cycloalkyl, heteroaryl or heterocycloalkyl, any of which may be optionally substituted.

2. The compound as recited in Claim 1, wherein:

R^1 is CH_2X^1;

X^1 is selected from the group consisting of CR^4R^5, $N(R^6)(R^7)$, $S(O)R^8$, $S(O)_2R^9$ or OR^{10};

R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are each independently selected from the group consisting of acyl, alkyl, alkylene, aminoalkyl, alkynyl, amido, amino, aryl, arylthio, carboxy, cycloalkyl, ester, ether, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylthio, heterocycloalkyl, heterocycloalkylthio, hydrogen, thio and sulfonyl, any of which may be optionally substituted; or, alternatively, R^6 and R^7 may combine to form heterocycloalkyl or heteroaryl, which may be optionally substituted;

A, B, C and D are each independently selected from the group consisting of acyl, alkoxy, alkyl, alkylene, alkylamino, alkynyl, amido, amino, aminosulfonyl, carboxy, ester, ether, halo, haloalkoxy, haloalkyl, hydrogen, imino, thio, sulfonate and sulfonylamino, any of which may be optionally substituted.

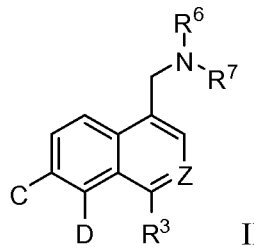
3. The compound as recited in Claim 2, wherein:

X^1 is $N(R^6)(R^7)$;

R^2 is hydrogen; and

A and B are both hydrogen.

4. The compound as recited in Claim 3, having structural Formula II:



II

or a salt, ester, or prodrug thereof, wherein:

Z is selected from the group consisting of N and N^+–O^-;

R^3 is selected from the group consisting of lower alkoxy, lower alkyl, halo, lower haloalkyl, cyano, and hydrogen, any of which may be optionally substituted;

R^6 and R^7 are each independently selected from the group consisting of acyl, alkyl, alkylene, aminoalkyl, alkynyl, amido, amino, aryl, arylthio, carboxy,

cycloalkyl, ester, ether, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylthio, heterocycloalkyl, heterocycloalkylthio, hydrogen, thio and sulfonyl, any of which may be optionally substituted; or, alternatively, R^6 and R^7 may combine to form heterocycloalkyl or heteroaryl, which may be optionally substituted; and

C and D are each independently selected from the group consisting of lower alkoxy, lower alkyl, halo, lower haloalkoxy, lower haloalkyl, and hydrogen, any of which may be optionally substituted.

5. The compound as recited in Claim 4, or a salt, ester, or prodrug thereof, wherein:

R^6 is selected from the group consisting of acyl, alkyl, alkylene, aminoalkyl, alkynyl, amido, amino, aryl, arylthio, carboxy, cycloalkyl, ester, ether, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylthio, heterocycloalkyl, heterocycloalkylthio, hydrogen, thio and sulfonyl, any of which may be optionally substituted; and

R^7 is selected from the group consisting of aryl and heteroaryl, either of which may be optionally substituted.

6. The compound as recited in Claim 5, wherein:

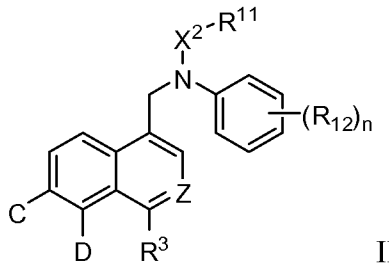
R^6 is X^2R^{11};

X^2 is selected from the group consisting of a bond, CH_2, C(O), and $S(O)_2$; and

R^{11} is selected from the group consisting of alkyl, amine, aryl, arylthio, cycloalkyl, haloalkyl, heteroaryl, heteroarylthio, heterocycloalkyl, and heterocycloalkylthio, any of which may be optionally substituted.

7. The compound as recited in Claim 6, wherein R^7 is phenyl.

8. The compound as recited in Claim 7, wherein the compound has Formula III:



III

or a salt, ester, or prodrug thereof, wherein:

Z is selected from the group consisting of N and $N^+–O^-$;

R^3 is selected from the group consisting of acyl, alkoxy, alkyl, amino, halo, haloalkyl and hydrogen, any of which may be optionally substituted;

X^2 is selected from the group consisting of a bond, CH_2, C(O), and $S(O)_2$; and

R^{11} is selected from the group consisting of alkyl, amine, aryl, arylthio, cycloalkyl, haloalkyl, heteroaryl, heteroarylthio, heterocycloalkyl, and heterocycloalkylthio, any of which may be optionally substituted;

R^{12} is halogen;

n is 0, 1, or 2; and

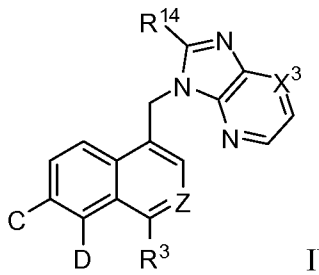
C and D are each independently selected from the group consisting of lower alkoxy, lower alkyl, halo, lower haloalkoxy, lower haloalkyl, and hydrogen, any of which may be optionally substituted.

9. The compound as recited in claim 8, wherein: C and D are each independently selected from the group consisting of fluoro and hydrogen.
10. The compound as recited in claim 8, wherein R^3 is selected from the group consisting of methyl, halo, cyano, and hydrogen, any of which may be optionally substituted.
11. The compound as recited in claim 10, wherein R^3 is hydrogen.

12. The compound as recited in Claim 8, wherein R^{11} is selected from the group consisting of lower aryl and lower heteroaryl, either of which may be optionally substituted.
13. The compound as recited in Claim 12, wherein R^{11} is selected from the group consisting of pyridine, pyrimidine, pyrazine, pyridazine, and thiazole, any of which may be optionally substituted with one or more substituents selected from the group consisting of hydrogen, halogen, and methyl.
14. The compound as recited in Claim 8, wherein X^2 is selected from the group consisting of a bond and CH_2.
15. The compound as recited in Claim 8, wherein R^{12} is chloro and n is 1.
16. The compound as recited in Claim 15, wherein said chloro is attached in the meta-position.
17. The compound as recited in Claim 4, wherein:

R^6 and R^7 combine to form heteroaryl, which may be optionally substituted; and

C and D are each independently selected from the group consisting of lower alkoxy, lower alkyl, halo, lower haloalkoxy, lower haloalkyl, and hydrogen, any of which may be optionally substituted.
18. The compound as recited in Claim 17, wherein the compound has structural Formula IV:



IV

or a salt, ester, or prodrug thereof, wherein:

Z is selected from the group consisting of N and $N^+–O^-$;

X^3 is selected from the group consisting of $C(R^{13})$ and N;

R^3 is selected from the group consisting of acyl, alkoxy, alkyl, amino, halo, haloalkyl and hydrogen, any of which may be optionally substituted;

R^{13} is selected from the group consisting of hydrogen, halogen, cyano, lower alkyl, lower alkoxy, lower amino, lower cycloalkyl, and lower heterocycloalkyl;

R^{14} is selected from the group consisting of alkyl, aryl, arylalkyl, amino, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, and heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of hydrogen, halogen, and methyl;

C and D are each independently selected from the group consisting of lower alkoxy, lower alkyl, halo, lower haloalkoxy, lower haloalkyl, and hydrogen, any of which may be optionally substituted.

19. The compound as recited in claim 18, wherein C and D are each independently selected from the group consisting of fluoro and hydrogen.
20. The compound as recited in claim 18, wherein R^3 is selected from the group consisting of methyl, halo, cyano, and hydrogen, any of which may be optionally substituted
21. The compound as recited in claim 20, wherein R^3 is hydrogen.
22. The compound as recited in claim 18, wherein R^{14} is selected from the group consisting of lower alkyl, lower aryl, lower arylalkyl, lower amino, lower cycloalkyl, lower cycloalkylalkyl, lower heteroaryl, lower heteroarylalkyl, lower heterocycloalkyl, and lower heterocycloalkylalkyl, any of which may be optionally substituted with one or more substituents selected from the group consisting of hydrogen, halogen, and methyl;
23. The compound as recited in claim 22, wherein R^{14} is selected from the group consisting of lower alkyl and lower cycloalkyl, either of which may be optionally substituted.
24. The compound as recited in claim 18, wherein R^{13} is selected from the group consisting of hydrogen and methyl.
25. A compound selected from the group consisting of Examples 1 to 21.
26. A compound or composition as recited in Claim 1 for use as a medicament.
27. A compound or composition as recited in Claim 1 for use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the inhibition of iNOS.
28. A pharmaceutical composition comprising a compound as recited in Claim 1 together with a pharmaceutically acceptable carrier.

29. A method of inhibition of iNOS comprising contacting iNOS with a compound as recited in Claim 1.
30. A method of treatment of a iNOS-mediated disease comprising the administration of a therapeutically effective amount of a compound as recited in Claim 1 to a patient in need thereof.
31. The method as recited in Claim 30 wherein said disease is selected from the group consisting of an inflammatory disease and a pain disorder.
32. The method as recited in Claim 31 wherein said inflammatory disease is selected from the group consisting of psoriasis, inflammatory bowel disease, rheumatoid arthritis, atopic dermatitis, asthma, and chronic obstructive pulmonary disorder.
33. The method as recited in Claim 31 wherein said pain is selected from the group consisting of neuropathic pain, migraine, and postsurgical pain.
34. A method of promoting wound healing in a patient in need thereof comprising the administration of a therapeutically effective amount of a compound as recited in Claim 1 to said patient.
35. A method of treatment of a iNOS-mediated disease comprising the administration of:
    a. a therapeutically effective amount of a compound as recited in Claim 1; and
    b. another therapeutic agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/054143

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D217/22 C07D401/12 C07D417/12 C07D487/04 A61K31/4704
A61K31/4709 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 584 379 A (WAGNER EUGENE R [US]) 22 April 1986 (1986-04-22) columns 4-5; claim 1; examples 1-3	1-5
X	US 2002/198205 A1 (HIMMELSBACH FRANK [DE] ET AL) 26 December 2002 (2002-12-26) paragraphs [0448], [0739], [1291], [2417]; claim 1	1-5, 26-35
X	WO 2005/092885 A (LILLY CO ELI [US]; BOULET SERGE LOUIS [US]; CLARK BARRY PETER [GB]; FA) 6 October 2005 (2005-10-06) Formula I, ex. 16 page 60	1-5
X	US 2002/006923 A1 (BARROW JAMES C [US] ET AL) 17 January 2002 (2002-01-17) compounds 3, 20, 21, 23	1-5

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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9 June 2008	23/06/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bareyt, Sébastian

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/054143

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 362 188 B1 (GUZI TIMOTHY [US] ET AL) 26 March 2002 (2002-03-26) columns 133-134	1-5
X	NISHIO, MASAHIRO ET AL: "HMN-1180, a small molecule inhibitor of neuronal nitric oxide synthase" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 287, no. 3, 1998, pages 1063-1067, XP002483360 table 1	1,2, 26-35
X	SOUTHAN, GARRY J. ET AL: "2-Aminopyridines. Novel inhibitors of nitric oxide synthases with potent pressure effects" PHARMACOLOGY COMMUNICATIONS , 7(4), 275-286 CODEN: PCMME9; ISSN: 1060-4456, 1996, XP009101227 table 1; compound 20	1,2, 26-35
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P,X	WO 2007/110237 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; ARISTA LUCA [AT]; HOEGENA) 4 October 2007 (2007-10-04) compoundss 21 page 18, 232 page 95 and 238 page 96	1-35

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Information on patent family members

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